LACK OF ASSOCIATIONS BETWEEN REST/ACTIVITY RHYTHMS AND COGNITION IN HEALTHY MIDDLE-AGED AND YOUNG ADULTS

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Understanding contributing factors to cognitive variation in healthy middle-aged and young adults may highlight mechanisms for interventions for pathologies of cognition and cognitive decline with age. Rest activity rhythms (RARs), as a proxy for variation in circadian functioning, have been related to normative variation in cognitive functioning among older adults. However, these findings have not yet been extended to young and middle-aged adults. The two following studies aimed to address this gap by investigating the relationship between RARs and cognitive functioning in middle-aged and young adults. Healthy middle-aged participants (n = 402, M = 42.9 year old, SD = 7.29) from the Adult Health and Behavior II project (n = 218; 54.1% female; Study 1) and healthy young adults (n = 109; M = 23.74 years old, SD = 3.32) from The Effects of Dose-Dependent Sleep Disruption on Fear and Reward Study (women n = 65; 56.9%; Study 2) underwent neuropsychological testing and wore an actiwatch. Actigraphy data was used to extract RAR measures for each participant and was quantified using both parametric (rhythm height and rhythm timing) and nonparametric techniques (day-to-day stability of rhythms and rhythm fragmentation). Regression models in Study 1 and robust regression models in Study 2 were used to statistically predict cognitive performance while controlling for several demographic, sleep, and health behaviors. In Study 1, individuals who exhibited RARs with a lower height also performed better in the verbal proficiency domain relative to those with higher, more robust RARs. *Post hoc* analyses suggest the association is partially mediated by job type. We speculate that sedentary midday behavior

required in certain jobs may obscure the circadian influence RARs. No other RAR and cognitive domain associations were found. Several factors that may contribute to the null results are considered, including using samples of convenience, potential masking of the circadian signal by sedentary job-related behavior, or the lack of a relationship between circadian variation and cognition. Additional research is required to confirm the possibility of masking by midday sedentary behavior and to test whether other measures of circadian functioning are related to cognitive performance in middle-aged and young adults.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

A big thank you to my family and friends who provided invaluable support and encouraging words throughout my graduate journey and to my advisor, Dr. Kathryn Roecklein, for her guidance through the process.

1.0 BACKGROUND AND SIGNIFICANCE

Cognitive performance is an important predictor of psychosocial functioning across the lifespan. Importantly, individuals experience a decline in cognitive performance as early as their mid-20s (Salthouse, 2009) and attenuated cognitive performance may be impactful during the young adult and middle-aged years, as it negatively affects scholastic performance, work performance, and everyday functioning. For instance, failures in attention and cognitive performance have been linked to poor SAT scores, poor reading comprehension, and poor college performance in young adults (Unsworth, Brewer, & Spillers, 2012; Unsworth & McMillan, 2013). Further, poor cognitive performance in middle-age has been associated with reduced work performance and increased risk for work burn out (Linden, Keijsers, Elings, & Van Schaijk, 2005). Additionally, poor attention has been related to increased risk for driving errors, violations, and motor vehicle accidents (Wickens, Tolpak, & Wiesenthal, 2008). Lastly, attenuated cognitive performance present during young adulthood may predict further cognitive decline later in life (e.g., Mehta, Yaffe, & Covinsky, 2002; Blacker et al., 2007). Overall, cognitive variation in young and middle-aged adults impacts individual achievement in school, work, and everyday functioning and may predict cognitive functioning later in life. Therefore, understanding mechanisms contributing to cognitive variation in healthy samples may have important implications in improving individual functioning and long term cognitive trajectories.

One potential under-explored and modifiable risk factor for cognitive variation in healthy samples may be individual variation in circadian functioning (Kyracou & Hastings, 2010; Schmidt, Peigneux, & Cajochen, 2012; Wright, Lowry, & LeBourgeois, 2012). The circadian system coordinates internal timing of processes via external cues (Welsh, Takahashi, & Kay, 2010) and has been shown to modulate daily cognitive functioning in individuals of all ages (e.g., Dijk, Duffy, & Czeisler, 1992). Further, disruption of the circadian system has been linked to attenuated cognitive performance (e.g., Silvia et al., 2010). Although these studies implicate the importance of circadian functioning in cognition across the lifespan, studies establishing a link between individual variation in circadian functioning, as captured by rest activity rhythms (RARs), and cognition, have been limited to elderly samples. Currently, no studies have investigated the association between individual variations in RARs and cognition in young or middle-aged adults. Associations between RARs and cognition in younger age samples would provide both a target for improving work and academic performance in healthy samples and implicate RARs as a potential modifiable mechanism in pathologies of cognition (i.e., traumatic brain injury or schizophrenia). Therefore, the proposed study aims to test associations between cognitive performance and circadian-related activity measures in young and middle-aged samples in order to provide preliminary evidence for a relationship between circadian variation and cognition in these age groups (see Figure 1).

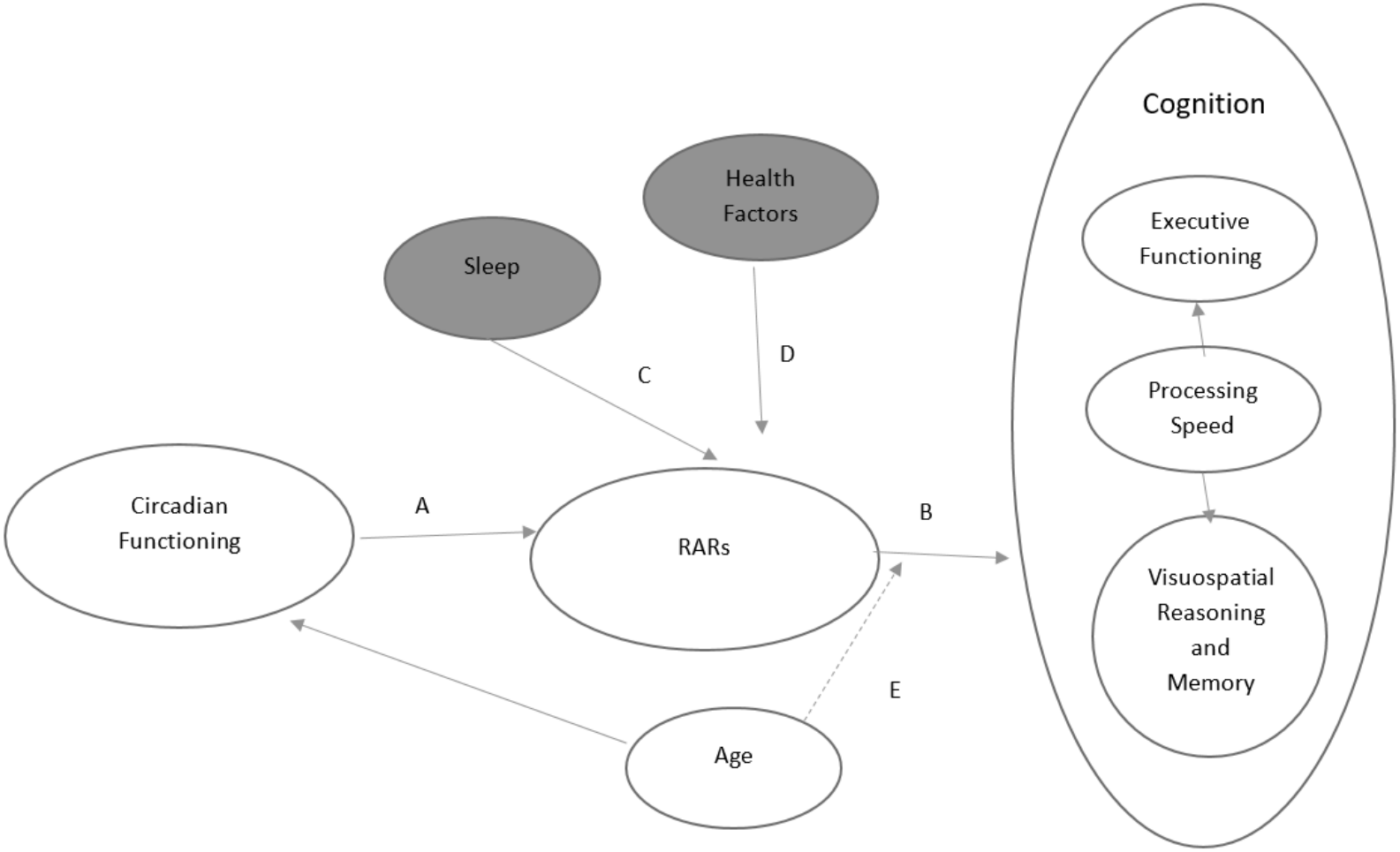

Figure 1. Model of the current proposal suggesting RARs represent circadian functioning and may predict executive functioning processing speed and visuospatial reasoning and memory.

1.1 CIRCADIAN FUNCTIONING

A brief review of the circadian system is warranted before describing the literature linking circadian functioning and cognition. Overall, the creation and maintenance of circadian rhythms is a complex process that involves the coordination of most body functions (for full review see Welsh, Takahashi, & Kay, 2010; Takahashi, Hong, Ko, & McDearmon, 2008). Circadian rhythms are oscillating processes that last approximately 24 hours and are ubiquitous throughout the body, coordinating a variety of bodily functions at every level, including the molecular, hormonal, and behavioral levels. Examples of common processes that exhibit a circadian rhythm include core body temperature, heart rate, cortisol levels, melatonin release, daily activity levels, and sleep/wake times. Circadian rhythms are created and maintained by the central clock located in the suprachiasmatic nucleus (SCN) in the hypothalamus. The main "zeitgeber" or entrainment cue received by the SCN is light, which is thought to help the body track environmental dawn/dusk cues. The SCN provides numerous types of signals to targets in the rest of the body, including the brain, liver, and gut (Buhr, Yoo, & Takahashi, 2010; Claustrat, Brun, & Chazot, 2005), to maintain rhythms peripheral to the central clock, essentially coordinating bodily processes. Further, the central clock is known to control the transcription and translation of 9% of the mammal genome (Akhatar et al., 2002), reflecting a broad impact of the circadian system on functioning (Silver & Kriegsfeld, 2014).

1.1.1 Measuring Circadian Variation

Given the pervasiveness of circadian rhythms, it is not surprising that variation in circadian rhythms has been shown to affect individual functioning across a number of domains (for review see Zelinski, Deibel, & McDonald, 2014). Circadian variation can be measured by capturing the rhythmic variation in SCN outputs and peripheral oscillators, like temperature, melatonin, expression of clock-controlled genes, and even behavior or activity. This information can be time sequenced and fit to a cosine curve in order to collect individual variation in acrophase and amplitude. Acrophase refers to the time of the peak of a circadian rhythm and reflects shifts in rhythms, either delayed or advanced. Conversely, amplitude describes the magnitude of the variation of the rhythm above and below the mean and reflects the robustness of the rhythm, either blunted or exaggerated. In addition to amplitude and acrophase, variation can be measured by the amount of fragmentation of a rhythm or how entrained a rhythm is to a 24-hour period. By capturing amplitude, acrophase, fragmentation, and 24-hour entrainment, researchers are able to quantify rhythmic variation within individuals in order to measure their circadian functioning.

1.1.2 Circadian Measures are Vulnerable to Masking

Importantly, circadian rhythms can also be "masked" by external influences that may prevent direct observation of circadian functioning via measures like melatonin and body temperature. Masking occurs when a non-circadian behavior is superimposed on, and obscures, behavior that is driven by the circadian clock (Aschoff, 1988). For instance, core body temperature has been shown to exhibit a defined circadian rhythm, which peaks during the day and reaches its nadir during the night hours (e.g., Wright, Hull, & Czeisler). However, if an individual is sick and

experiencing a fever in response to inflammation, this SCN controlled rhythm of the core body temperature will be obscured by the fever. Therefore, collecting temperature rhythm in an individual who has a fever will yield an inaccurate reflection of their circadian functioning. Other examples of masking include, exposure to artificial light that may mask underlying melatonin rhythms created by the SCN (e.g., Honma, Honma & Wada, 1987) or social interactions that may influence rhythms separate from master clock (e.g., Wever, 1988; Monk et al., 1991). The issue of masking requires researchers to carefully interpret results and to control for confounding measures in order to parse direct contributions of the circadian system relative to other masking influences.

1.1.3 Broad Impact of Circadian Functioning

Individual variation in circadian functioning has been associated with poor outcomes including mood disorders (Germain & Kupfer, 2008; Hasler, Buysee, Kupfer, & Germain, 2010; Li et al., 2013), cardiovascular disease (Paudel et al., 2011), cancer (Stevens, 2005; Gery & Keffler, 2010), insulin resistance (Leproult, Holmback, &Van Cauter, 2014; Wong, Hasler, Kamarck, Muldoon, & Manuck, 2015), and mortality (Tranah et al., 2010). Taken together, evidence suggests that healthy circadian functioning is crucial for both physical and mental health, and may therefore support optimal cognitive functioning.

1.2 CIRCADIAN FUNCTIONING AND THE IMPACT ON COGNITION

The current literature indicates that the circadian system impacts cognitive functioning and supports hypotheses that individual variation of circadian rhythms may be associated with normative cognitive performance. Specifically, studies indicate that the circadian system modulates normative cognitive performance and that direct manipulation of circadian rhythms in animal models impacts brain morphology and cognition in animals. Further, preliminary studies investigating presumed circadian disruption in vulnerable samples (i.e., shift workers), indicate that these groups also exhibit lower circadian performance than others. Lastly, measuring aberrant circadian functioning in humans suggests a link between circadian variation and cognitive performance. Each of these lines of evidence are reviewed below and suggest that natural variation in individual circadian rhythms may be associated with cognitive functioning.

1.2.1 Aspects of Cognition Have a Circadian Rhythm

First, forced desynchrony studies suggest that the circadian system creates a circadian rhythm in some cognitive functions. The circadian system has been shown to impact cognition throughout the lifespan, via two separate paths. First, it indirectly impacts cognition by regulating sleep timing and structure (Dijk & Czeisler, 1995; Dijk & Lockley, 2002), both of which have been related to cognitive performance (Edinger, Glenn, Bastian, & Marsh, 2000; for review see Sculin & Bilwise, 2015). Second, the circadian system is thought to modulate cognition directly via morphological and neurochemical changes in the brain (Kyracou & Hastings, 2010). In an attempt to uncouple the impact of sleep and circadian functioning to better understand their independent impact on cognition, forced desynchrony studies force individuals to deviate from

normal 24-hour periods by extending sleep-wake cycles to 28 hour periods or shortening them to 20 hour periods. By extending or shortening periods, forced desynchrony designs allow for the temporal separation of homeostatic sleep drive and circadian rhythms influencing sleep and alertness, while maintaining adequate sleep duration. These types of studies have consistently found an independent effect of the central clock. Specifically, many have found a circadian rhythm in cognition in young, middle-aged, and older adults, suggesting that the central clock contributes to the variation in cognition (Burke, Scheer, Ronda, Czeisler, & Wright, 2015; Darwent et al., 2010; Dijk, Duffy, & Czeisler, 1992; Silvia et al., 2010; Santhi et al., 2016; Wyatt, Cecco, Czeisler, & Dijk, 1999; Wright, Hull, & Czeisler, 2002; Zhou et al., 2011). Interestingly, a circadian modulation of the effect of sleep deprivation has also been documented (Lo et al., 2012), further supporting an intricate relationship between circadian variation and sleep on cognition. Importantly though, forced desynchrony studies have been completed in small samples (n = 6 to 36), mostly in men, and are executed in a laboratory setting, limiting their generalizability.

In somewhat larger samples, testing individuals outside of peak time of alertness has aimed to better understand how circadian variation may impact cognition. Specifically, individuals experience individual differences in timing of peak alertness and testing participants outside of this peak leads to a decrement in cognitive functioning. Importantly, a mismatch between testing period and peak alertness attenuates performance in both young adults and older adults (May, Hasher, & Stotlzfus, 1993; May & Hasher, 1998; Wincur & Hasher, 2002; Rowe, Hasher, & Turcotte, 2009 for review see Maire, Reichert & Schmidt, 2013), further implicating a circadian modulation of cognition. Together, growing evidence suggests the circadian system modulates cognitive performance across the lifespan.

1.2.2 Animal Models Linking Circadian Disruption and Cognition.

Animal research has demonstrated that direct manipulation of circadian rhythms attenuates cognitive performance and changes brain morphology. Rats exposed to lighting schedules that cause circadian shifts exhibit poor performance on both learning where a platform is during the Morris Water Maze task, remembering where that platform is hours to days later (Devan et al., 2001), and recognizing when that platform has been moved (Craig & McDonald, 2008; Karatsoreos, Bhagat, Bloss, Morrison, & McEwen, 2011; Zelinski, Hong, & McDonald, 2014). Additionally, hamsters exposed to a lighting schedule that made them permanently arrhythmic were unable to differentiate between novel and familiar objects 20 and 60 minutes after training (Ruby et al., 2008). Photoperiod shifts are related to decreases in dendritic branching and complexity of neurons located in the prefrontal cortex and the hippocampus, areas that are known to be involved in a wide range of cognitive processes (Cho et al., 2000; Fonken, Kitsmiller, Smale, & Nelson, 2012; Loh et al., 2010; Karatsoreos et al., 2011). In sum, circadian disruption has been shown to be mechanistic in cognitive impairments using animal models.

1.2.3 Human Evidence Linking Circadian Variation to Attenuated Cognitive Performance

In addition to the literature documenting circadian rhythms of cognition in adults and the cognitive consequences of direct circadian disruption in animals, preliminary studies suggest that humans that are exposed to schedules that cause circadian disruption may also exhibit attenuated cognition performance compared to those not exposed to such schedules. Middle-aged shift workers have been shown to exhibit attenuated cognitive performance (Åkerstedt, 1998; Ansiau,

Wild, Niezborala, Rouch, & Marque, 2008), which is amplified by the amount of years an individual worked shifts (Marquie, Tucker, Folkard, Gentil, & Ansiau, 2014). Shift workers' biological clocks are often unable to adjust to their constantly shifting wake and sleep rhythms (Dumont, Benhaberou-Burn, & Paquet, 2001; Reinberg et al., 1987), creating desynchrony between wake times and circadian rhythms in sleep propensity. This suggests that circadian disruption may be the mechanism linking shift work to decreased cognitive functioning. Additionally, social jet lag, or the difference in circadian rhythms on days in which an individual has socially imposed rhythms (e.g., workdays) and those they do not (e.g., non-workdays), may predict lower academic performance. Specifically, undergraduates with larger differences between free days and work days achieved lower overall grades at the end of the semester (Haraszti, Ella, Gyöngyösi, Roenneberg, & Káldi, 2014). Together, studies that assume individuals experience circadian disruption, via shift work and social jet lag, have linked circadian functioning and cognition.

1.2.4 Natural Circadian Variation and Cognition

Although current evidence suggests that the circadian system modulates cognitive functioning in animals and humans, little research has investigated the relationship between naturally occurring variation in circadian rhythms and cognition. One, recent study demonstrated that reduced melatonin secretion predicted lower performance on an intelligence test (Waller et al., 2016), providing more direct evidence that variation in endogenous circadian rhythms influences variation in cognitive functioning. Although this study suggests the impact of circadian disruption in the cognitive functioning across the lifespan, very few studies have explored the impact of natural variation in rhythms on cognition. As described below, studies that have

investigated the association between circadian variation and cognition has been mostly limited to older adults. The lack of studies investigating circadian variation in the young and middle-aged adults highlights a gap in the current research.

1.3 REST/ACTIVITY RHYTHMS AND COGNITION

Diurnal fluctuations in the timing of rest and activity, or rest/activity rhythms (RARs), is thought to represent the underlying circadian organization of these rhythms (for a review see Ancoli-Isreal et al., 2003; Littner et al., 2003, Path A; Figure 1) and may provide important insight into the connection between natural variation in rhythms and cognition. RARs are collected noninvasively via actigraphy and quantified by estimating amplitude or acrophase and/or capturing overall daily stability and fragmentation (for example see Figure 3). Daily activity rhythms in animals have been shown to be made arrhythmic after the ablation of the SCN, significantly disturbing sleep/wake times that normally coincide with light/dark cues (Rusak, 1977). Importantly, activity rhythms are restored after SCN tissue is replaced (Lehman et al., 1987; Silver, Lehman, Gibson, Gladstone, & Bittman, 1990), suggesting the SCN is causally involved in the generation of daily activity rhythms and timing of sleep and wakefulness. Further, RARs respond to known entrainment signals including light/dark cues (Pollak, Tyron, Nagariaja, & Dzwonczyk et al., 2001) and melatonin (Laste et al., 2013; Laakso, Lindblom, Leinonen, & Kaski, 2007), indicating that RARs are sensitive to the same cues that are known to entrain both the SCN and peripheral circadian targets. Additionally, RARs have been shown to be correlated with several other circadian rhythms, including core body temperature and melatonin in sighted individuals (Middleton, Arendt, & Stone, 1996; Younstedt, Kripke, Elliot,

& Klauber, 2001) and in the blind who lack the ability to detect light entraining information (Lockley, Skene, Butler, & Arendt, 1999), indicating that RARs respond similarly to light as do other known circadian rhythms in the body. Interestingly, a recent study suggests post-mortem differences in SCN neural cell types have been related to differences in amplitude of activity rhythms (Wang et al., 2015), suggesting that changes in the SCN are correlated with changes in RARs. Overall, RARs capture circadian-related daily activity rhythm information and respond in similar ways as other circadian variables, demonstrating that RARs are an effective measure of circadian functioning. Therefore, RARs provide an important measure to capture the link between circadian functioning and cognition (Figure 1; Path B).

Importantly, the majority of RARs have been measured in older samples or in pathological samples. For instance, in older samples, RARs have been associated with higher mortality rates, depression, Alzheimer's disease, and cardiovascular disease (Paudel et al., 2010; Paudel et al., 2011; Smagula et al., 2015; Witting et al., 1990). In addition, aberrant RARs have been associated with schizophrenia, attention-deficit/hyperactive disorder, and bipolar disorder (e.g., Hauge, Oedgaard, Holsten & Fasmer, 2010; Harper et al., 2004; Jones, Hare, & Evershed 2005; Van Veen et al., 2010 for review see Gonçalves, Adamowicz, Louzada, Moreno, & Araujo, 2015). Although some of these studies include healthy controls for comparison, they lack a depth of an investigation into healthy RAR functioning. Exploration into RAR variation in healthy young samples would extend the current literature in order to better understand how RARs may change over the lifetime (Haung et al., 2002).

Consistent with the rest of the literature, a limited literature currently exists investigating the association between RARs and cognitive domains in healthy individuals. Importantly, these studies have controlled for important confounding and masking factors including sleep and

health factors that may affect RARs and do not originate from the circadian system (see Figure 1; Paths C&D). For instance, sleep structure, duration, and quality may be more influenced by factors independent of the SCN and may also impact RARs. Indeed, objectively and subjectively assessed sleep duration, as well as sleep quality, has been associated with both stability and fragmentation of the RAR, indicating that sleep may impact the variation in RARs (Luik et al., 2013).

Additionally, health factors, including both physical and mental health, are associated with RARs. For example, body mass index, cardiovascular health, and depressive symptoms have been associated with RAR variation (Luik et al., 2013; Walsh et al., 2014). Although these relationships between sleep and health factors are likely bi-directional (e.g., physical health affects daily activity and daily activity affects physical health), the significant associations with RARs highlight these as important factors to control while trying to isolate circadian functioning in RARs. While controlling for these factors, RAR-cognition studies have found associations in several cognitive domains, including processing speed, executive functioning, and visuospatial reasoning and memory.

1.3.1 Processing Speed

Processing speed, which has been associated with RAR variation, is thought to be a measure of cognitive efficiency and represents the ability to rapidly perform low-skill tasks. Particularly important in these domains are attention and concentration, which allow for focused and speeded performance. Further, processing speed effects performance on higher order cognitive domains, including working memory (Salthouse, 1994; Salthouse, 1996). Commonly used assessments to measure processing speed include timed trials of visual search and speeded reading. For

example, slower performance on Trail Making Test A (Reitan & Wofson, 1985), which requires individuals to quickly connect numbers, reflects impaired processing speed. Additionally, the Stroop task (Golden, 1978), which requires individuals to quickly name colors or read color words, is also commonly used to assess processing speed, with slower times reflecting impaired processing speed. These tasks capture and individuals' ability to quickly process information, a skill that depends on attention and concentration, and is thought to be foundational to other higher order domains such as executive functioning.

Importantly, RARs have been shown to significantly predict processing speed measures. For instance, reduced amplitude and fragmented rhythms (i.e., higher alteration between rest and activity), but not reduced stability of rhythms across days, were associated with slower processing speed (Oosterman et al., 2009). Consistent with these findings, Lim et al., (2012) found that higher fragmentation of both rest and activity was associated with slower processing speed above and beyond the total duration of rest and activity periods. Lastly, in a group of individuals 45 years old and up, both increased fragmentation and lack of day-to-day stability of RARs statistically predicted slower processing speed even after controlling for sleep and several health factors (Luik et al., 2015a; see Table 1). Together, evidence suggests the association between the circadian components of RARs in older samples and slower processing speed. Notably, this is consistent with the larger circadian literature, which suggests that attention and vigilance exhibit a circadian rhythm (Dijk, Duffy, & Czeisler, 1992; Wright., Hull, & Czeisler, 2002; Valdez, Ramírez, García, Talamantes, & Cortez, 2010), neural circuitry that controls attention is modulated by the circadian system (Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Aston-Jones, Gonzalez, & Doran, 2007), and circadian disruption impairs attention, vigilance, and processing speed performance (Cohen et al, 2010; Silvia et al., 2010; Anderson, Campbell,

Amer, Grady & Hasher, 2014). Therefore, current evidence suggests a link between RARs and processing speed performance in healthy samples.

Table 1. RAR Studies Investigating Associations with Cognitive Domains

Paper	Mean Age	Study Design	RAR Analysis Approach	Covariates	Cognitive Domains Associated
Oosterman et al., 2009	69.5	Cross-Sectional	Non Parametric Parametric	Gender Age Diabetes Hypertension Hypercholesterolemia Cardiovascular Disease Smoking	Processing Speed Executive Functioning (I, S) Visuospatial Memory
Lim et al., 2012	82.4	Cross-Sectional	Non Parametric	Age Gender Education Total Activity Total Rest	Processing Speed Executive Functioning (I,S,W) Visuospatial Reasoning
Walsh et al., 2014	82.8	Longitudinal	Parametric	Age Gender Education BMI Depressive symptom Use of Antidepressants Caffeine use Physical Activity Sleep Duration Sleepiness History of : Coronary Heart Disease, Chronic Obstructive Pulmonary Disease, Hypertension, Diabetes, Stroke	Executive Functioning (I, S)
Luik et al., 2015	62	Cross-Sectional	Non Parametric	Gender Age Employment Status Education Depressive Symptoms BMI Activities of Daily Living Stroke Myocardial Infarction Diabetes, Possible Sleep Apnea Sleep Onset Latency Wake After Sleep Onset Total Sleep Time Sleep Quality	Processing Speed Executive Functioning (I, S)

Note. Table includes all studies which investigate associations between RARs and cognitive domains. Associations listed in table are those that were significant after adjustment for the listed covariates. BMI = Body Mass Index, I= inhibition, S= Set shifting, W= working memory

1.3.2 Executive Functioning

Additionally, a preliminary link between RARs and executive functioning has been established. Executive functioning is often separated into three separate domains, which include set shifting, inhibition, and working memory performance (Miyake et al., 2000). Shifting is defined as the ability to switch between tasks or mental sets. For example, in Trail Making Test B, individuals are asked to draw lines switching between numbers and letters in numerical and alphabetical order, respectively. This task requires the individual to switch between determining which letter is next alphabetically and determining which number comes next in sequential order. Inhibition is defined as the ability to inhibit a dominant or automatic response when required. The most common assessment of inhibition is the Color-Word task of the Stroop (Golden, 1978), in which a participant is presented with color words printed in different color ink and asked to say the ink color and inhibit reading the word. Lastly, working memory refers to the ability to remember and update information being held in short term memory. Working memory is often assessed using a form of the Digit Span assessment (e.g., Wechsler, 1997), which requires individuals to repeat verbally presented numbers in exact order, repeat numbers backward, or reorganize numbers in numerical order. The latter two tasks require individuals to be able to both hold the number verbally presented in memory and then reorganize them in some way, invoking working memory. Together, set shifting, inhibition, and working memory are important components of executive functioning and have also been associated with circadian functioning and RARs.

RARs studies have found associations between abnormal and fragmented RARs and executive functioning tasks. For instance, Walsh et al., 2014 found that lower amplitude, reduced

robustness, and later acrophase of RARs predicted lower executive functioning, (including individual performance on the Trail Making Task B task) after controlling for sleep and an extensive list of health factors in older women. Cross-sectional studies in older individuals controlling for sleep (Lim et al, 2012; Luik et al., 2015) and health factors (Oosterman et al., 2009; Lim et al, 2012; Luik et al., 2015) have also detected an association between greater variation of rhythms day-to-day, greater fragmentation, and lower amplitude and lower performance on executive tasks. For instance, more fragmented and less stable rhythms have been associated with poorer performance on the Stroop Color-Word task relative to those with less fragmented and more stable rhythms, suggesting that disrupted circadian rhythms may lead to impaired response inhibition. (Luik et al., 2015; Oosterman et al., 2009). Consistent with this finding, lower amplitude has been associated with poorer performance on the Stroop task in individuals with schizophrenia (Bromundt et al., 2011). The relationship between aberrant RARs and executive functioning are consistent with chronobiological studies demonstrating that working memory and inhibitory control exhibit circadian rhythms (Burke et al., 2015). Moreover, circadian disruption in adult mice has been shown to produce morphological changes in the prefrontal cortex, an area that supports executive functioning (Collette, Hogge, Salmon, & Van der Linden, 2006). Further, this morphological change in the prefrontal cortex was also found to be related to impaired set shifting performance (Karatsoreos et al., 2011). Together, evidence suggests an association between variation in RARs and executive functioning in healthy samples.

1.3.3 Visuospatial Reasoning and Memory

Lastly, visuospatial reasoning and memory has been linked to RAR variation. Visual reasoning refers to the ability to mentally manipulate images. For instance, Block Design tasks included in intelligence assessments like the Wechsler Adult Intelligence Scale (e.g., Wechsler, 1997) require individuals to replicate presented pictures with provided blocks. In order to successfully build each picture, the participant must be able to manipulate the blocks in order to replicate the target stimuli. When assessing visuospatial memory, or the ability to remember where objects are in space, researchers often use a design memory task like the Brief Visuospatial Memory Test (Benedict & Groninger, 1995). This task requires individual to recreate six designs with proper drawing and placement for each object. Therefore, visuospatial reasoning and memory depends on the individual's ability to mentally orient objects.

Although fewer studies have investigated the impact of circadian disruption and RARs on visuospatial abilities, the current literature suggests a link. Lim et al., (2012) found that lower performance on visuospatial manipulation tasks were associated with significantly more fragmented RARs after controlling for sleep variables. Further, Oosterman et al., (2009) found an association between a design memory task and fragmented rhythms after controlling for health factors, suggesting that individuals with more fragmented RARs performed more poorly at remembering and completing designs. These findings are consistent with findings in the circadian animal literature. Rats exposed to circadian disruption exhibit morphological changes in the hippocampus that is thought to support visuospatial memory performance (Gibson, Wang, Tjho, Khattar, & Kriegsfeld, 2010; Fonken et al., 2012), and perform poorly on both acquisition (Craig & McDonald, 2008) and retention phases (Craig & McDonald, 2008; Zelinski et al.,

2014) of the visuospatial task for the Morris Water Maze. Overall, the current literature links RARs and visuospatial abilities.

In summary, a limited literature links variation in RARs with cognitive domains in healthy samples. Importantly, all of these studies only examine this association in older samples (Lowest mean age = 62 years old; see Table 1) and fail to explore the association between RARs and cognition in young and middle-aged samples. Understanding the potential impact of variation in RARs on cognition in young and middle-aged samples may be particularly important due to the impact of cognitive performance on school and work achievements. Further, the broader chronobiological literature summarized above implicates the circadian system in impacting cognitive performance, across the lifespan, including young and middle-aged individuals. Given that current studies investigating RARs are limited to elderly individuals, the lack of studies in young and middle-aged adults represents a gap in the literature. Therefore, to address this gap, the current study proposes to investigate the association between RARs and these cognitive domains, while controlling for other potential confounding factors, to provide evidence for the impact of circadian disruption on cognitive performance in young and middle-aged adults.

1.4 INTERACTION OF AGE AND CIRCADIAN VARIATION AND THE IMPACT ON COGNITION

The present study additionally aims to address a potential interaction of age and RARs, and how this may impact cognition (see Path E, Figure 1). It is known that cognition changes over the lifespan and usually begins to decline in the mid-20s (Salthouse, 2009; Salthouse, 2011) and age

impacts circadian functioning and, in turn, RARs (Liberman, Wurtman, & Teicher, 1989; Youngstedt, Kripke, Ellliot, & Kauber, 2001; Luik et al., 2013), though it remains unclear how age and RARs may interact over the lifespan. The only study to investigate the interaction between RARs and age found that the relationship between fragmented rhythms and worsened executive functioning was strongest in elderly individuals (Luik et al., 2015). This interaction was not evident when looking at processing speed tasks or global cognition, suggesting that the moderating effect of age may be specific to executive tasks. However, because this study did not include individuals below the age of 45, it may have missed important moderation effects exhibited in younger individuals. The findings reported by Luik et al. (2015) are consistent with studies that administered cognitive tests outside of participants' peak timing of arousal. Specifically, in studies investigating inhibitory responses and working memory, older individuals are more affected by being tested out of their peak time than younger individuals, suggesting older individuals' executive functioning may be more vulnerable to desynchrony effects (May & Hasher, 1998; Matchock & Mordkoff, 2009).

In contrast, younger individuals may be more sensitive to disruptions in RARs, specifically in the domains of processing speed and visuospatial ability. Chronic misalignment between sleep and temperature rhythms was associated with increasing lapses of attention with each successive cycle of misalignment in younger individuals, while older individuals remained relatively stable (Silvia et al., 2010). Further, in a comparison between young and older adults who were awoken every 10 minutes throughout a sleep period, younger individuals performed worse on both math and attention tasks relative to older participants (Bonnet, 1989). Although it is not possible to disentangle the contributions of sleep and circadian disruption in Bonnet (1989), the results suggest that younger individuals are more vulnerable to the cognitive impacts

of sleep fragmentation. Consistent with Silvia et al. (2010), younger individuals with disrupted and abnormal rhythms had larger impairments in attention relative to older individuals (Bonnet, 1989). Further, younger individuals performed more poorly on a visuospatial memory task administered outside of their peak arousal time relative to older individuals, suggesting that younger individuals' visuospatial functioning may be more vulnerable to desynchrony effects (Rowe, Hasher, & Turcotte, 2009). In combination, these studies suggest that age moderates the relationship between circadian disruption and cognitive functioning, such that RAR variation may affect executive tasks to a greater extent in older individuals and affect processing speed and visuospatial abilities to a greater extent in younger individuals. However, no study has investigated an interaction between RARs and age in younger samples, a goal of the present study.

2.0 STUDY 1

2.1 AIMS AND HYPOTHESES

The current study proposes to fill the gaps in the current literature by investigating associations between RARs and cognitive functioning in young and middle-aged adults. Specifically, Study 1 variables include measures of processing speed, executive functioning (switching and inhibition), working memory, visuospatial abilities, verbal learning and memory and verbal proficiency. Given the evidence highlighting an association between RARs and processing speed, visuospatial reasoning and memory, and executive functioning associations discussed above, these were considered primary cognitive domains and it was predicted that RARs would be associated with these domains. In contrast, the current literature would suggest that RARs, after controlling for sleep variables, would not be related to verbal learning and memory as well as verbal proficiency domains. It was predicted that RARs would not be associated with verbal proficiency as it is usually considered a stable reflection of the intelligence quotient (IQ), a factor that is not hypothesized to be related to circadian regulation of RARs. Further, it was predicted that RARs would not be associated with verbal learning and memory, as this domain has been established in the literature as more likely associated with sleep and not with circadian disturbances (Stickgold, 2013) and was not found to be associated with RARs in a previous study in an older sample (Luik et al., 2015). As an additional aim, given the potential interactive effect

of age and disrupted RARs on cognitive functioning, a moderation effect of age was tested in a large, sufficiently powered middle-aged sample. The specific aims for the project were as follows:

1. To test whether parametric rhythm measures of RARs including amplitude, acrophase, and robustness of rhythm are associated with primary cognitive domains and not secondary domains. It was predicted that individuals with lower amplitude, later acrophase, and less robust rhythms would have lower scores for processing speed, executive functioning, and visuospatial abilities relative to those with larger amplitudes, earlier acrophase, and more robust rhythms. It was also predicted that amplitude, acrophase, nor rhythm robustness would not be significantly related to verbal learning and memory nor verbal proficiency domains.
2. To test whether non-parametric measures of RARs including both day-to-day variation and the amount of fragmentation of RARs are associated with primary cognitive domains and not with secondary domains. It was predicted that higher variability between days and greater fragmentation would be associated with lower scores for processing speed, executive functioning, and visuospatial abilities relative to those with more day-to-day stability and less fragmentation. It was also predicted that neither day-to-day variation nor the amount of fragmentation of RARs would not be significantly related to verbal learning and memory nor verbal proficiency domains.
3. To explore a potential interaction between age and RARs in statistically predicting cognitive performance. It was predicted that the executive

performance of older individuals would be more affected by disrupted RARs than younger individuals and the processing speed and visuospatial abilities of younger individuals would be more affected by disrupted RARs than older individuals. A significant interaction was not predicted for secondary domains.

2.2 METHODS

2.2.1 Participants and Design

Participants ages 30 to 54 were drawn from the Adult Health and Behavior Project – Phase 2 (AHAB-II), a study of psychosocial, behavioral, and biological risk factors for subclinical cardiovascular disease in healthy individuals. Individuals were excluded if they (a) had a history of cardiovascular disease, schizophrenia or bipolar disorder, chronic hepatitis, renal failure, major neurological disorder, chronic lung disease, or stage 2 hypertension (BP ≥ 160/100 mm Hg); (b) had a chronic psychiatric history, (c) reported drinking 5 or more drinks 3-4 times per week; (d) took fish-oil supplements (because of the requirements for another substudy); (e) were prescribed insulin or glucocorticoid, anti-arrhythmic, antihypertensive, lipid-lowering, psychotropic, or prescription weight-loss medications; (f) were pregnant; or (g) were shift workers. Informed consent was obtained in accordance with the guidelines of the University of Pittsburgh Institutional Review Board. Participants completed several in-laboratory visits, including a neuropsychological assessment visit that occurred from 0 to 139 days before or after

actigraphy. Demographic, mood, and health covariate data were also collected over multiple laboratory visits.

2.2.2 Neuropsychological Assessment

During a separate lab visit, individuals were administered a battery of neuropsychological assessments. Confirmatory factor analysis was completed in order to create factor scores (spatial reasoning, working memory, processing speed, verbal proficiency, verbal learning and memory, and executive functioning), which confirmed previously constructed factors in the AHAB II sample (Marsland et al., 2015). Domains of interests are listed first and were hypothesized to have a relationship with RARs. Additional secondary domains that were not hypothesized to be associated with RARs are also included. Assessments were grouped in domains in the following way:

2.2.2.1 Primary domains

Processing speed. Processing speed was indexed using Trail Making Test A (Reitan & Wofson, 1985) completion time and the first two sections of the Stroop Color-Word test (Golden, 1978). Trail Making Test A requires participants to connect numbered dots in order as fast as they can. The first two subtests of the Stroop test required participants to read a list of color names and then name color, regardless of color of type, as fast as possible.

Working memory. The Digit Span subtest from the Wechsler Adult Intelligence Scale- III (WAIS-III; Wechsler, 1997a) and the Spatial Span subtest from the Wechsler Memory Scale III (WMS-III; Wechsler, 1997b) were used to quantify verbal and non-verbal working memory. The Digit Span subtest requires participants to repeat verbally presented random number sequences

of increasing length in forward and reverse order. During the Spatial Span, participants were presented with a series of spatial patterns on a three dimensional board and then participants were asked to repeat the series forward and backward.

Executive function. The executive functioning domain contains both the Trail Making Test B and the response inhibition portion of the Stroop Color-Word Test. In Trail Making Task B, individuals were asked to connect dots of alternating numbers and letters as fast as they can. In order to obtain a measure of mental flexibility independent of the processing speed, Trail Making Task A time will be subtracted from Trail Making Task B time. The third portion of the Stroop test, which requires participants to name the color of the ink of color words which are incongruent, will provide information about individual response inhibition. Further, an interference score will be calculated from the previous two portions ([portion 2* portion 1]/ [portion 1 + portion 2]) and then subtracted from the third portion performance.

Visuospatial reasoning. Visuospatial reasoning was assessed using the Block Design and Matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI, 1999). The Block Design task requires participants to reproduce a picture using red/white blocks within a set time limit. The Matrix Reasoning task required participants to choose a response option that completes an uncompleted matrix.

2.2.2.2 Secondary Domains

Verbal proficiency. The Vocabulary and Similarities subtests of the WASI were used to calculate the verbal proficiency domain. The Vocabulary subtest required participants to define words verbally. In the Similarities subtest, participants were presented with two different words and asked to report how they are similar.

Verbal learning and memory. The Rey Verbal Learning test (Rey, 1958) and the Four Word Short Term Memory test (Kobayashi, Nakano, Tago, & Niwa, 2010) were used to create the verbal learning and memory domain. The Rey Verbal Learning test requires participants to recall as many of a 15-word list that is verbally presented. The complete task consists of five trials with the original list, an interference list, and a recall trial of the original list. During The Four Word Short Term Memory Test a participant was read four unrelated words and then a three-digit number. Then the participant was asked to count backwards by threes from the number given for 5, 15, or 30 seconds, depending on the trial. Then, participants were asked to recall the four words originally presented.

2.2.3 Actigraphy Collection, Preprocessing and Analysis

2.2.3.1 Actigraphy collection and actigraph cleaning

Participants were asked to wear an Actiwatch (Philips Respironics; USA) in AHAB II for seven days and were instructed to wear the watch even when showering. The participant was also asked to wear the watch on at least one non-work day during the monitoring period. Data was cleaned using Actiware software using automated thresholds. Specifically, the wake threshold selection was set to medium and the sleep interval detection algorithm was programmed to detect sleep epochs of more than 10 minutes. Watch-off time was identified as a 30 minute or longer period of time with activity counts at zero. Algorithm derived sleep variables including total sleep time (TST) and wake after sleep onset (WASO) were included as covariates in analyses.

2.2.3.2 Actigraphy data preprocessing

Individual data files including 60 second epoch activity data were exported into text files using the Actiware software. Files were cleaned first to delete any unnecessary data (e.g., daily summaries) and excluded epochs (e.g., watch off time). Files were then individually cleaned and formatted in unique manners for the extended cosine and nonparametric analyses.

2.2.3.3 Modeling RARs

2.2.3.3.1 Cosinor Analysis

Cosinor Analysis. Cleaned activity data was used in an extended sigmoidal form of cosinor analysis (Marler, Gehrman, Martin, & Ancoli-Israel, 2006). The most often used equation for cosine modeling is:

$$r(t) = mes + amp * cos(\frac{[t-\phi]2\pi}{24})$$

where r(t) represents the modeled solution, mes (mesor) represents the middle of the data, amp (amplitude) is the maximum the model deviates from above and below the mesor, phi represents the time of day that of the maximum value of the model. Although this model fits some circadian rhythms well, including core body temperature, cosine curves may misrepresent data that reflect more of a squared rhythm (e.g., activity rhythms). For the current study, we used the anti-logistic function to extend the cosine curve to a squared form. The following represents the anti-logistic function:

$$l(x) = \exp(\beta[x-\alpha]) / \{1 + \exp(\beta[x-\alpha])\}$$

And extended the cosine curve if x is substituted for the cosine curve:

$$c(t) = \cos(\frac{[t-\phi]2\pi}{24})$$

Which can then be simplified and inserted into the cosine curve model as:

$$r(t) = \min + amp * l(c(t))$$

The resulting equation includes five parameters that represent the shape and variation of the squared sinusoidal curve (phi = acrophase, min = minimum value of the function, amp = amplitude, β = the "steepness" of the curves relative to the cosine wave, and α = the width of the trough relative to the width of the peaks).

Additionally, a pseudo *F* statistic was calculated using the residuals of the equation to give an estimate of fit. From the five parameter extended sigmoidal transformed cosine model, acrophase, amplitude, and the pseudo *F* statistic was used to estimate phase time, rhythm variation, and overall rhythmicity in regression models to predict neuropsychological assessment scores.

To run these analysis, syntax was developed in SAS Version 9.4 (SAS Institute Inc., 2014; Cary, NC) and the individual parameters were extracted for each participant. Amplitude, acrophase, and the pseudo *F* statistic were used as independent variables in analyses.

2.2.3.3.2 Nonparametric Analysis

Nonparametric analyses allow for the calculation of both interdaily stability (IS) and intradaily variability (IV). Nonparametric analyses have been argued to better capture variation in RARs as they do not make assumptions about the rhythms shape (Witting, Kwa, Eikelenboom, Mirmiran, & Swaab, 1990; van Someren et al., 1996). Interdaily stability refers to the extent in that RARs on individual days resemble each other. Importantly, IS may capture similar RAR variability

information as calculating social jet lag (e.g., the difference in rhythms between workday and non-workday) due to its ability to capture daily differences in rhythms, though IS provides broader variability information as it is not restricted to capturing work and non-workday differences. IV refers to the amount of fragmentation of daily RARs. To calculate IS, a signal-to-noise ratio was created between the variance of the 24-hour activity rhythm pattern around the mean over the overall variance of activity. Specifically, the following equation was used:

$$IS = \frac{n\sum_{h=1}^{p}(\overline{x_h} - \bar{x})^2}{p\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

Where n represents the total number of data points, p represents the number of data collected per day, $\overline{x_h}$ represents the minute means of activity, $\bar{x}$ is the mean of all of the data, and x_i represents individual data points of activity counts. IS then reflects the amount of day-to-day variation in activity rhythms. Lower IS scores indicate higher day-to-day variation.

To calculate IV, a ratio was created as the mean squared first derivative of the data over the overall variance of activity. The following equation was used:

$$IV = \frac{n\sum_{i=2}^{n}(x_i - x_{i-1})^2}{(n-1)\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

IV then reflects the frequency of transitions between rest and activity (e.g., fragmentation). A higher IV measure reflects greater fragmentation of the RARs.

To calculate the nonparametic measures, cleaned data was imported into R Studio (R Studio Version 1.0.136 (R Studio Inc, 2015; Boston, MA) using the nparACT package (Blume, Santhi & Schabus, 2016). The variables IS and IV were extracted from this analysis and used as independent variables in analyses.

2.2.4 Covariates

Education, age, race, and gender were collected and used as covariates due to their previous association with cognitive outcomes and rhythm measures (e.g., Luik et al., 2013, Luik et al., 2015). Education was included and quantified as number of years of school. Race was categorized as Caucasian (reference group) and non-Caucasian and included as a covariate. In addition, the following covariates were selected *a priori* due to their association with RARs, cognition, and their standard use in the literature.

Time of testing. Given the potential time of day effects on cognitive performance (e.g., May & Hasher, 1998), time of testing was used as a covariate in analyses. Time of testing was identified as the start time of Sensus (a series of computer administered questionnaires), which directly proceeded the neuropsychological assessment. Importantly, because the WASI and the remaining neuropsychological battery were administered on two different visits, there were two different testing times employed as covariates depending on the cognitive domain being tested. The "WASI" testing time was used for verbal proficiency and visuospatial reasoning. The "second" testing time was used for the remaining models predicting cognitive domains

Employment status. Although participants were excluded if they were unemployed, individuals were categorized as full-time or part-time workers with full time as the reference type. This variable was included in the model as individuals with full time employment may exhibit more stable rhythms.

Physical activity. Because physical activity has been associated with improved cognition (Ratey & Loehr, 2011) and may be a confounding factor affecting both activity rhythm measures and cognition, overall activity was included as a covariate. To capture average weekly physical activity, average weekly kilocalories expended was claculated using the Paffenbarger Physical

Activity Questionnaire (Paffenbarger Jr, Blair, Lee, & Hyde, 1993). This questionnaire has high reliability (Ainsworth et al., 1993) and correlates highly with objective measures of fitness (Nowak et al,. 2010).

Sleep variables. Average total sleep time (TST) was included as a covariate to control for the known impacts of sleep duration on cognition and likely impact on activity rhythms (Scullin & Bliwise, 2014). Further, wake after sleep onset (WASO) may impact cognition directly due to the impact on sleep continuity or may reflect the impact of circadian misalignment with sleep homeostasis (e.g., Wilckens et al., 2014a). In order to ensure that the association between RARs and cognition was not solely due to fragmented to sleep, WASO was used as covariate. Both TST and WASO were extracted from actigraphy, which are thought to be an accurate reflection of both sleep duration and wake time after sleep onset as measured by the gold standard of polysomnography (Marino et al., 2013).

Body mass index (BMI). Participant's height and weight were collected during an in-laboratory visit and used to calculate BMI, which was used as a covariate given previous associations between BMI and RARs (Luik et al., 2013) and BMI and cognition (Sabia, Kivimaki, Shipley, Marmot & Singh-Manoux, 2009).

Depression. Due previous RAR association with depression (Smagula et al., 2013), depression was originally proposed as a covariate. The Center of Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) was used to measure overall depression symptom number and severity. Higher scores on the scale represent more severe depressive symptomology. A maximum score is a 60. The CES-D has moderate (r = 0.45-0.70) test-retest reliability and moderate correlations between scores and ratings of depression severity by nurses

(r = 0.56; Radloff, 1977). The sleep item was subtracted from the total score in order to avoid overlap with the sleep covariates to prevent the confounding of sleep and depressive symptoms.

Alcohol consumption. Alcohol was included as a covariate due to its known effects on the master clock (Spangel, Rosenwasser, Schumann, & Sarkar, 2005), the potential effects on RARs and cognition, and the common use of alcohol use as a covariate in RAR analyses (e.g., Paudel et al., 2010). Total number of alcoholic beverages were included in the analyses as a covariate.

Smoking status. Given previous associations with RARs and smoking (Luik et al., 2013) smoking status was used as a covariate. Individuals self-identified as having never smoked, or as ex-smokers, or current smokers.

AHAB II included a total of 502 individuals. Of those individuals, 12 participants were excluded because they only had actigraphy data and 24 participants were excluded because they did not have usable actigraphy data (i.e., watch malfunction or not collected). Forty-eight participants were excluded because they did not have complete neuropsychological assessment data and six individuals were missing covariate data. Finally, ten individuals were excluded because did not have at least four days of actigraphy available for analysis. Four days was used as a cut off as a balance between current norms in the RAR literature (one to seven days; Berger et al., 2007; Luik et al., 2013) and available data.

2.2.5 Statistical Approach

First, in order to create factors that were consistent with previous literature published using the same sample, confirmatory factor analysis was completed using raw z scored data using the CFA function in the lavaan package (Rosseel, 2012) in R Studio version 1.0.136 (R Studio Inc, 2015). To limit the impact of outliers, variables of interest were winsorized to range across a maximum

of three standard deviations (Field, 2013). Weekly activity, CES-D, and amplitude were positively skewed and were log transformed. Correlations were then run between study covariates, rhythm measures, and cognitive factors.

To investigate Aim 1, a hierarchical regression model with four steps was created to test the association between extended cosine rhythm measures and each of the cognitive factors (see Table 2). Step one included demographic factors age, gender, education, employment status and testing time. Step two included activity and sleep factors, average weekly activity, WASO, and TST. Step three included the health factors BMI, daily alcohol consumption, and smoking status. Finally, step four included acrophase and amplitude. As described below, *F* correlated highly with amplitude and was included in separate analyses. In order to investigate differential association between primary cognitive domains of interest and differential domains, a model was created for each cognitive domain. Due to the overall lack of significant associations between CES-D, cognitive factors, and rhythm measures, the CES-D was excluded from analyses. To investigate Aim two, the same hierarchical regression models were created with the exception that in step four the nonparametric measures, IV and IS were included. To investigate Aim three, an interaction term between any rhythm measures found to be significant in 1 or 2 and age was included as Step 5. We created models for both the primary cognitive domains that were hypothesized to be associated with RARs, and for the secondary domains that were hypothesized to not be associated with RARs. All statistical analyses other than the data reduction (confirmatory factor analysis; CFA) were completed in SPSS version 24 (IBM, 2016; Armonk, NY). Assumptions for all linear regression models were checked and met. In order to correct for the six models run per aim, Benjaminin & Hochberg alpha level correction (Benjamini &

Hochberg, 2000; Benjamini & Hochberg, 1995) was used to determine significance (corrected p value of p =0.009 per study aim).

Table 2. Regression Models with Covariates for Each Aim

Blocks	Aim 1a and Aim 2a: Cosinor Analysis	Aim 1b and 2b: Nonparametric Analysis
1: Demographic	Age	Age
	Gender	Gender
	Education	Education
	Race	Race
	Employment Status	Employment Status
	Time of Testing	Time of Testing
2: Sleep and Activity	Activity Measure	Exercise Measure
	Wake After Sleep Onset	Wake After Sleep Onset
	Sleep duration	Sleep duration
3. Health Factors	Weekly Alcohol	Weekly Alcohol
	Smoking Status	Smoking Status
	BMI	BMI
	Mood Variable	Mood Variable
3: RAR variables	Amplitude	Interdaily stability
	Acrophase	Intradaily variability

Note. Variables included in hierarchical regression models for Aims 1 and 2. Health and sleep factors selected both on previous associations with RARs (e.g. Walsh et al., 2014; Luik et al, 2015) and factors collected in the AHAB II sample and SFeRe sample. Mood variable was the CES-D in AHAB II and PHQ9 in SFeRe.

The study covariates represent slight changes from the originally proposed model. Following further reading of the literature, the proposed covariates were modified by including employment status and smoking status due to their impact on RARs (Luik et al., 2013) and their use in previous literature linking RARs and cognition (Luik et al., 2015, Oosterman et al., 2009). The original proposed model is reviewed in Appendix A, though patterns of findings did not differ from the findings reported below.

2.2.6 Neuropsychology Data Reduction

Factors were estimated using *z* scored data organized by the above cognitive domains that were previous determined using exploratory factor analysis in the same sample (Marsland et al., 2015). After allowing for residual variation to correlate in subtests originating from the same neuropsychological tests (e.g., Stroop Color, Stroop Word, Stroop Color-Word and Stroop Interference score), the comparative fit index (CFI) = 0.97, the Tuker –Lewis fit index (TFI) = 0.96 indicating an excellent fit and the root mean square error of approximation (RMSEA) = 0.06 indicated an adequate fit between the model and the observed data (Hu & Bentler, 1999). See Table 3 for standardized factor loadings and standard errors. Unit-weighted averages of the standardized subtest scores (factor scores) were extracted and used as the primary dependent variable for analyses. In all cases, higher factor scores were equivalent to better performance.

Table 3. Means for Subtests and Factor Loadings Confirmatory Factor Analysis

Factor	Subtests	Means	Standardized Estimate	Standard Error
Visual Spatial Reasoning				
	Matrix	27.05 (4.01)	0.778	0.044
	Blocks	47.43 (15.00)	0.836	0.043
Working Memory				
	Spatial Span Forward	8.19 (1.82)	0.562	0.051
	Spatial Span Backward	7.67 (1.76)	0.751	0.048
	Digit Span Forward	10.71 (2.21)	0.499	0.051
	Digit Span Backward	7.78 (2.48)	0.645	0.048
Verbal Learning				
	Rey A7	10.88 (3.38)	0.617	0.051
	Rey B1	6.17 (1.94)	0.599	0.051
	Four Word correct	37.14 (10.03)	0.822	0.049
Executive				
	Trail Making Test Difference	29.76 (15.77)	-0.582	0.053
	Stroop Color-Word	44.44 (9.51)	0.47	0.055
	Stroop Interference	0.64 (7.44)	0.637	0.053
Processing Speed				
	Trail Making Test A	23.09 (6.69)	-0.436	0.054
	Stroop Color	76.63 (12.12)	0.386	0.056
	Stroop Word	103.61 (18.25)	0.34	0.056
Verbal Proficiency				
	Vocabulary	65.00 (8.31)	0.876	0.046
	Similarities	39.28 (4.05)	0.771	0.047

Note. Means of each subtest listed with standard deviation in parenthesis.

2.3 RESULTS

Overall the sample had an average age of 42.95 (*SD* = 7.29) years old, was mostly employed full time, in the overweight range for BMI, and reported minimal depression. The median income for participants was $65-79,999 and the majority were married or had a life partner (63.3%). Refer to Table 4 for summary demographics for the 402 participants included in analyses. Table 4 also includes averages for the sleep variables (WASO and TST), extended cosine variables (amplitude, acrophase, *F*), and nonparametric measures (IV and IS) for reference. Table 3 includes subtest averages that reflect average to high average performance on all cognitive tasks. Actigraphy data ranged from 4 to 11 days, with an average of 8 days. Pearson's correlations between covariates and cognitive factors are summarized in Table 5. Age, gender, education, average weekly physical activity, WASO, BMI and smoking status were all significantly correlated with at least some of the cognitive factors. Those who were older, male, less educated, had lower activity, experienced more wake after sleep onset, had higher BMI, and were current smokers were more likely to have lower cognitive scores than the rest of the sample.

Table 4. Demographics for AHAB II Sample (*n* = 402)

Variables	Mean	SD
Age	42.95	7.29
Female, n (%)	218 (54.1%)	
Non-Caucasian, n (%)	70 (17.4%)	
Participant Income*	$65-79,999	
Married, n (%)	255 (63.3%)	
Years of School	16.9	2.81
Part-time Employment, n (%)	44 (10.9%)	
Weekly Calorie Expenditure	2993.43	2546.79
BMI	26.83	5.09
CES-D	7.66	7.45
Weekly Alcohol	3	4.29
Current Smoker, n (%)	60 (14.9%)	
TST	356.01	50.98
WASO	51.53	18.63
Amplitude	150.13	78.62
Acrophase	14:57	1:08
F	5243.89	4548.29
IV	0.79	0.21
IS	0.44	0.17

Note: Categorical variables listed as number of individuals and percent in parentheses. SD = standard deviation, BMI = body mass index, CES-D = Center of Epidemiological Studies Depression Scale, TST= Total sleep time, WASO= wake after sleep onset, IV= intradaily variability, IS = interdaily stability, * median income

Table 5. Covariates and RAR Correlations with Cognitive Factors

Variable	Amplitude	Acrophase	F	IS	IV	Visuospatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal proficiency
Age	-0.13**	-0.18**	-0.10*	0.03	-0.02	-0.31**	-0.32**	-0.26**	-0.31**	-0.30**	-0.13**
Gender	0.08	-0.12*	-0.16**	0.11*	-0.14**	-0.20**	-0.18**	-0.05	-0.15**	-0.16**	-0.17**
Years of Education	-0.08	<0.01	-0.13*	-0.06	0.26**	0.40**	0.34**	0.36**	0.35**	0.35**	0.53**
Race	-0.15**	0.12*	-0.11*	-0.12*	0.02	-0.49**	-0.47**	-0.38**	-0.48**	-0.49**	-0.46**
Employment	-0.01	0.15**	-0.05	-0.04	-0.06	-0.08	-0.06	-0.04	-0.08	-0.08	-0.12*
WASI Testing Time	-0.01	0.05	-0.02	-0.06	-0.03	0.02	0.01	0.04	0.00	0.00	0.06
Second Testing Time	-0.11*	0.10	-0.06	-0.12*	0.06	-0.08	-0.09	-0.05	-0.09	-0.07	-0.01
Weekly Calorie Expenditure	0.17**	-0.02	0.08	-0.01	-0.03	0.16**	0.16**	0.07	0.15**	0.16**	0.12*
WASO	-0.22**	0.03	-0.16**	-0.01	-0.02	-0.18**	-0.18**	-0.12*	-0.17**	-0.18**	-0.12*
TST	-0.06	-0.02	-0.15**	0.06	0.04	0.08	0.09	.125*	.103*	.099*	0.08
BMI	-0.16**	-0.02	-0.02	-0.02	-0.02	-0.22**	-0.19**	-0.16**	-0.20**	-0.19**	-0.21**
CES-D	-0.02	0.08	-0.03	-0.01	-0.01	-0.05	-0.05	-0.08	-0.05	-0.06	-0.05
Weekly Alcohol	0.04	0.06	0.04	-0.07	-0.05	0.09	0.10	0.10	0.11*	.104*	0.09
Smoking Status	0.04	0.12*	0.09	0.01	-0.17**	-0.18**	-0.14**	-0.19**	-0.14**	-0.14**	-0.23**

Note. BMI = body mass index, CES-D = Center of Epidemiological Studies Depression Scale, TST= Total sleep time, WASO= wake after sleep onset, IV= intradaily variability, IS = interdaily stability,** $p<0.01$, *$p<0.05$

2.3.1 Aim 1: Extended Cosine Analyses

For four participants, the cosine analyses were excluded due to inability of the model to converge, leaving 398 individuals in the extended cosine analyses. Examples of both high and low amplitude, and earlier and later acrophase, are depicted in Figure 2 and 3, respectively. Correlations between rhythm measures revealed that the measure of fit, pseudo *F*, correlated highly with amplitude ($r = 0.64$, $p < 0.001$) and was therefore unable to be included in the same regression models. Further analyses did not reveal added value of models exploring the pseudo *F* statistic separately (i.e., the *F* coefficient was not statistically significant in any of the cognitive factor models. See Appendix B for results) and therefore analyses with the pseudo *F* statistic are not included in the results.

No significant correlations were found between extended cosine measures and cognitive factors. In order to gain an understanding of how activity rhythms may have been affected by the study covariates, Pearson's correlations between both extended cosine measures and study covariates were completed (Table 5). Of note, age was significantly correlated with amplitude and acrophase. Lower amplitude and earlier acrophase was associated with older age ($r = -0.13$, $p = 0.01$; $r = -0.18$, $p < 0.0001$ respectively), as expected. Pearson's correlations between rhythm measures and cognitive factors are summarized in Table 6.

Table 6. Correlations between Cognitive Factors and RARs

Variable	Visuospatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal proficiency
Amplitude	0.02	0.04	0.02	0.04	0.04	-0.07
Acrophase	0.03	0.03	<0.01	0.02	0.03	0.03
F	0.02	0.03	-0.03	0.02	0.03	-0.05
IS	0.01	0.01	-0.01	0.01	0.00	-0.04
IV	0.11*	0.08	0.15**	0.09	0.09	0.22**

Note. IV= intradaily variability, IS = interdaily stability ** $p<0.01$, *$p<0.05$

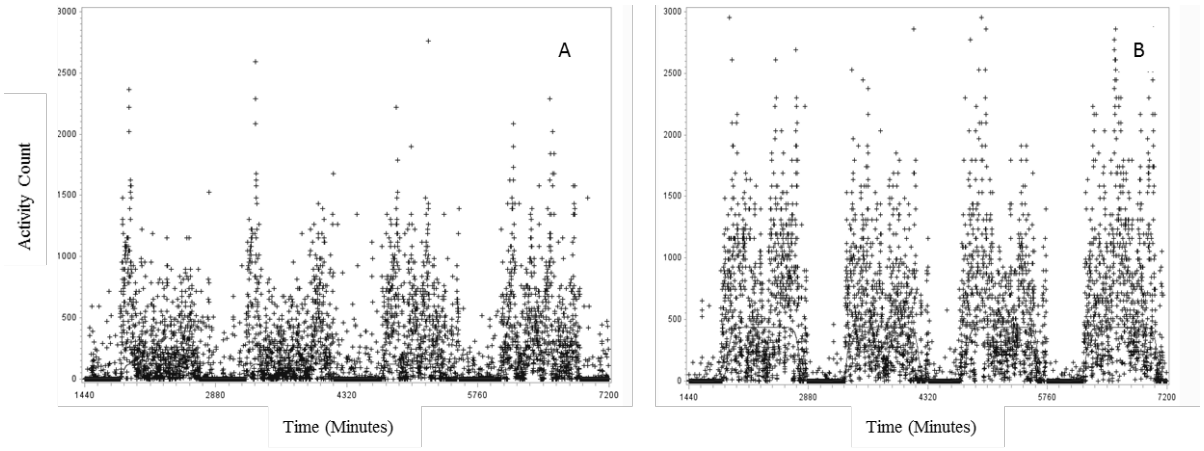

Figure 2. Comparison between low and high amplitude in Study 1. A. Depicts a participant in Study 1 who exhibited a low amplitude (45) B. Depicts an individual with a high amplitude (374)

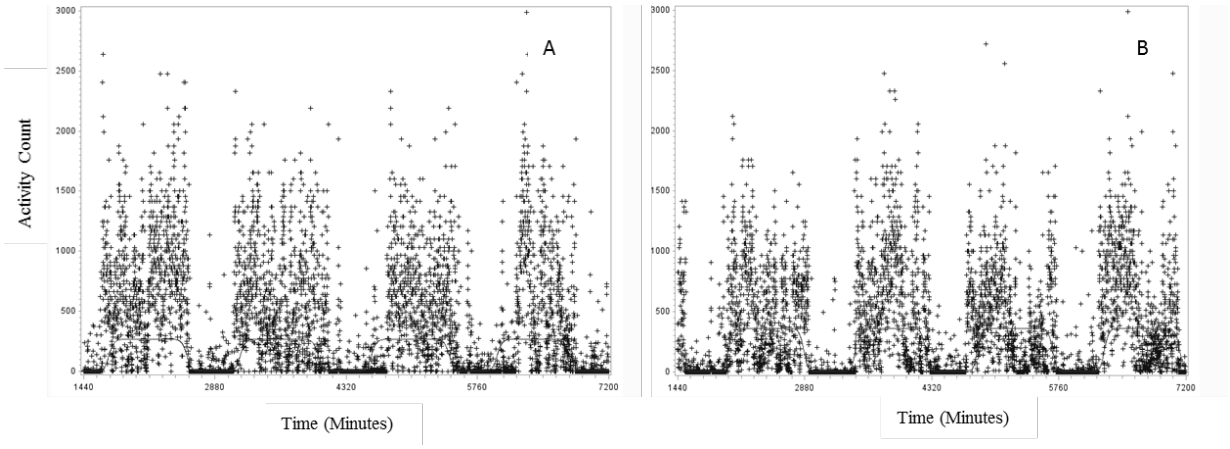

Figure 3. Comparison between early and late acrophase in Study 1. A. Represents a participant with an early acrophase at 12:17. B. Depicts a participant with a later acrophase at 19:11

2.3.1.1 Hierarchical regression models

Hierarchical regression models testing the associations with cognitive factors including demographic variables (step one), sleep and activity variables (step two), and health factors (step three) and extended cosine measures (step four) were constructed. All models for each step were significant at $p < 0.0001$. R^2 and ΔR^2 for each step for each hierarchical regression model predicting the cognitive factors are listed in Table 7. For each model, step one predicted a significant amount of variance in the cognitive factors. Step two and three did not change R^2 significantly.

Table 7. R^2 and ΔR^2 for Primary Analyses Predicting Cognitive Factors

Model Steps	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Extended Cosine						
Step one	0.398***	0.349***	0.256***	0.353***	0.355***	0.427***
Step 2	0.009	0.009	0.003	0.008	0.010	0.003
Step 3	0.005	0.003	0.010	0.005	0.004	0.010
Step 4	0.006	0.003	0.001	0.004	0.005	0.016**
Nonparametric						
Step one	0.400***	0.353***	0.260***	0.356***	0.358***	0.424***
Step 2	0.009	0.009	0.003	0.008	0.010	0.003
Step 3	0.005	0.003	0.010	0.005	0.003	0.010
Step 4	0.001	<0.001	0.007	0.001	0.001	0.010*

Note. Step one included demographic factors age, gender, years of school, employment status and testing time. Step 2 included activity and sleep factors, average weekly activity, wake after sleep onset, and total sleep time. Step 3 included health factors, BMI, daily alcohol consumption, depression, and smoking status. Step 4 included respective RAR measures. Step one row includes R^2 and all other Steps include ΔR^2. Due to the differences in sample size between the extended cosine and the nonparametric approaches, R2 varied slightly between extended cosine and nonparametric models. *** $p < 0.001$, ** $p < 0.01$, *$p<0.05$.

The WASO coefficient was the only additional coefficient that remained significant above and beyond demographic variables at each step in the visuospatial reasoning (step two: β = -0.09, p = 0.02 ;step three: β = -0.09, p = 0.03), processing speed (step two: β = -0.09, p = 0.03;step three: β = -0.09 p = 0.03), and working memory (step two: β = -0.09, p = 0.03 ;step three: β = -0.09, p = 0.03) models. The exception was the third step of the executive functioning model, which was trending (step three: β = -0.08, p = 0.051), though WASO coefficient in the second step was significant (step two: β = -0.08, p = 0.04). Overall, WASO, when added to the model in step two, was significantly related to all primary cognitive domains.

Primary domains: visuospatial reasoning, processing speed, executive functioning, working memory. Amplitude nor acrophase coefficients were significant in step four of the primary cognitive factors (Table 8). However, WASO was significant in the fourth step of the visuospatial reasoning (β = -0.10, p = 0.01), processing speed β = -0.10, p = 0.02), working memory (β = -0.10, p = 0.01), and executive functioning (β = -0.09, p = 0.03) models.

Table 8. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Extended Cosine Analyses For Cognitive Factors

Variable	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.03 (-0.21)*** 0.01	-0.03 (-0.24)*** 0.01	-0.02 (-0.18)*** 0.01	-0.03 (-0.23)*** 0.01	-0.03 (-0.22) *** 0.01	0.01 (-0.04) 0.01
Gender	-0.14 (-0.08) 0.08	-0.11(-0.06) 0.08	0.08 (0.04) 0.09	-0.05 (-0.03) 0.08	-0.07 (-0.04) 0.08	-0.08 (-0.04) 0.07
Race	-0.94 (-0.39)*** 0.10	-0.92 (-0.38)*** 0.11	-0.69 (-0.29)*** 0.11	-0.90 (-0.39)*** 0.11	-0.92 (-0.39)*** 0.11	-0.78 (-0.33)*** 0.10
Testing Time	<0.01 (0.01) <0.01	<0.01 (-0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.05) <0.01
Years of School	0.08 (0.25) *** 0.01	0.07 (0.21)*** 0.01	0.08 (0.25)*** 0.02	0.07 (0.21)*** 0.12	0.07 (0.21)*** 0.01	0.13 (0.42)*** 0.01
Employment Status	-0.07 (-0.02) 0.12	0.01 (0.01) 0.12	0.02 (0.01) 0.13	-0.06 (-0.02) 0.10	-0.06 (-0.02) 0.12	-0.24 (-0.08) 0.11
Weekly Activity	0.09 (0.04) 0.10	0.12 (0.05) 0.11	-0.04 (-0.02) 0.11	0.10 (0.04) 0.01	0.13 (0.06) 0.10	0.04 (0.02) 0.10
WASO	-0.01 (0.10)* 0.01	-0.01 (-0.10)* 0.01	-0.01 (-0.05) 0.01	0.01 (-0.09)* 0.01	-0.01 (-0.10)* 0.01	-0.01 (-0.07) 0.01
TST	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.03) <0.01	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.03) <0.01
BMI	-0.01 (-0.06) 0.01	-0.01 (-0.03) 0.01	-0.01 (-0.01) 0.01	-0.01 (-0.03) 0.01	-0.01 (-0.02) 0.01	-0.01 (-0.05) 0.01
Smoking Status	-0.05 (-0.04) 0.05	-0.01 (-0.01) 0.05	-0.10 (-0.08) 0.06	-0.01 (-0.01) 0.05	-0.01 (-0.01) 0.05	-0.10 (-0.09)* 0.05
Weekly Alcohol	0.01 (0.04) 0.01	0.01 (0.06) 0.01	0.02 (0.08) 0.01	0.01 (0.07) 0.01	0.01 (0.06) 0.01	0.01 (0.05) 0.01
Amplitude	-0.13 (-0.08) 0.07	-0.10 (-0.06) 0.07	-0.07 (-0.04) 0.08	-0.10 (-0.07) 0.07	-0.10(-0.06) 0.07	-0.19 (-0.11)** 0.07
Acrophase	0.04 (0.04) 0.04	0.02 (0.02) 0.04	0.01 (0.01) 0.04	0.02 (0.03) 0.04	0.03 (0.04) 0.04	0.07 (0.08) 0.03

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.001$) BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset. *** $p<0.001$, ** $p< 0.01$, *$p<0.05$

Secondary domains: verbal proficiency and verbal learning. Amplitude nor acrophase was associated with verbal learning in step 4 of the model. Although not significant when tested using zero-order Pearson's correlations, the fourth step added a significant amount of variance to the model ($F_{(14, 397)}$ = 22.85, ΔR^2 = 0.02, p <0.001) and amplitude was significantly correlated with verbal proficiency above and beyond other covariates (β = -0.11, p = 0.006; Figure 4A). This association was not expected and further investigated in *post hoc* analyses (pg. 40). Importantly, this verbal proficiency and amplitude association does survive correction for the six models using Benjamini & Hochberg correction (corrected p value = 0.009).

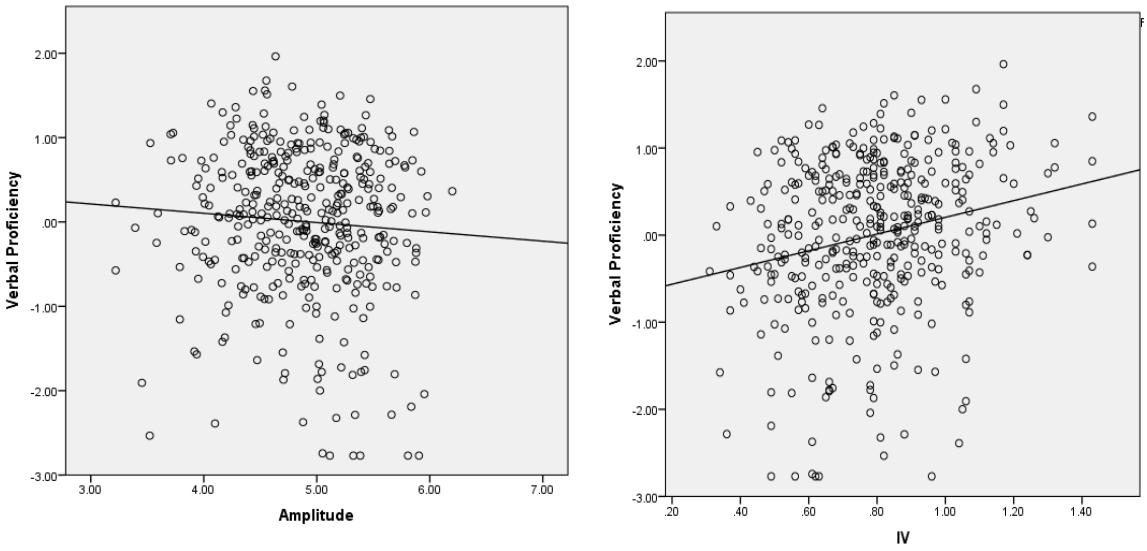

Figure 4. Significant correlations between RAR measures and verbal proficiency. A. Relatively small but significant correlation between amplitude and verbal proficiency. B. Larger association between IV and verbal proficiency.

2.3.2 Aim 2: Nonparametric Analyses

Nonparametric analyses included all 402 participants. See Figures 5 and 6 for examples of participants exhibiting high and low IS and IV. In order to gain an understanding of how activity rhythms may have been affected by the study covariates, Pearson's correlations between non-parametric measures and study covariates were run (Table 5). Both IS and IV were not significantly correlated with age. Interestingly, IV was significantly correlated with years of education (r = 0.26, p < 0.0001), such that individuals with more years of education exhibited higher daily fragmentation of their RARs. This was surprising in that more years of education might have been expected to be associated with higher cognitive functioning, and therefore less fragmentation. Pearson's correlations between rhythm measures and cognitive factors are summarized in Table 6. No significant correlations were found between rhythm measures and cognitive factors with the exception that IV was significantly associated with visuospatial

reasoning, verbal learning, and verbal proficiency (r = 0.11, p = 0.03; r = 0.15, p < 0.01; r = 0.22, p < 0.0001 respectively). Importantly, this correlation was opposite of the predicted direction such that those who exhibited more RAR fragmentation performed lower in these cognitive domains relative to those individuals who exhibited less fragmentation.

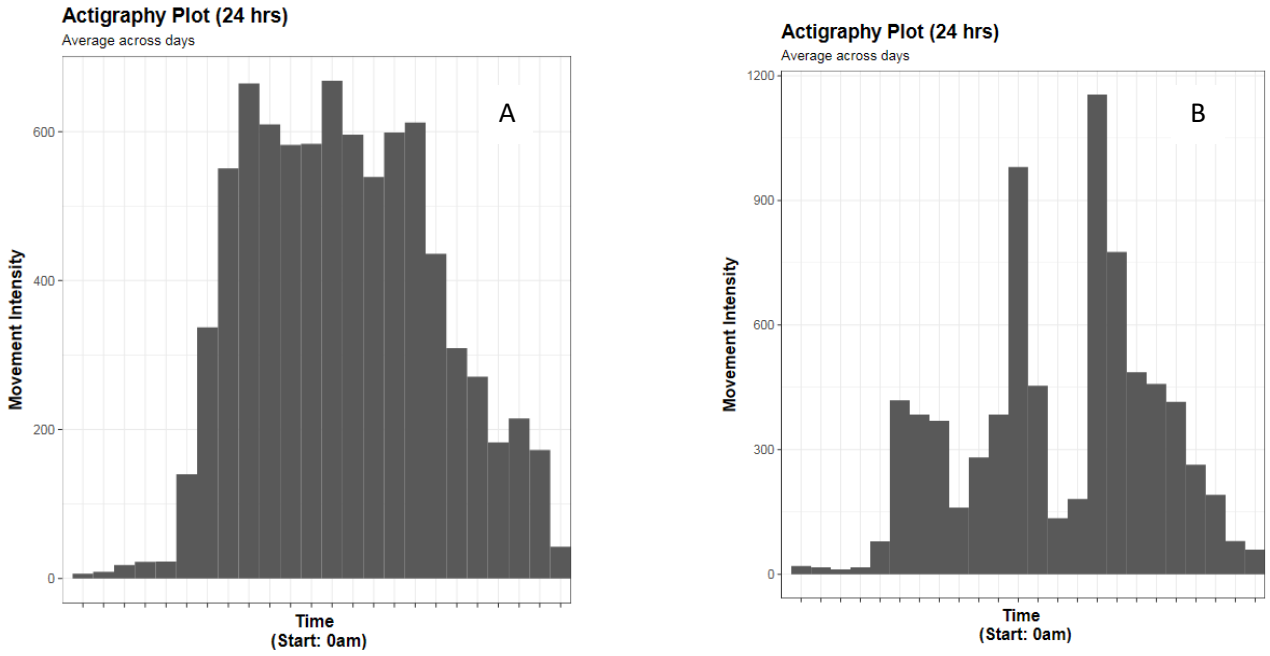

Figure 5. Comparison of low and high IV in Study 1. A. Depicts an individual who had low IV (0.3) in the sample. While, B. depicts a participant who represents a high IV in the sample (1.43).

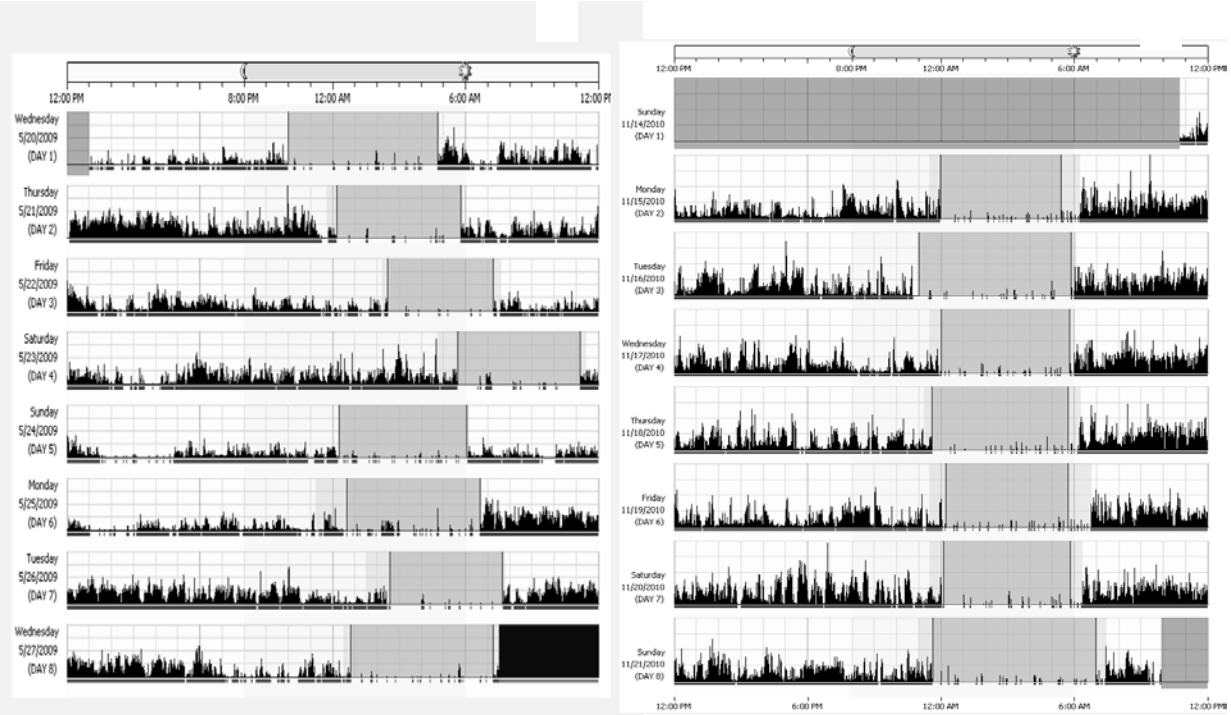

Figure 6. Actigraph comparisons between individuals with highest and lowest IS in Study 1I. A. Actigraph from participant A who had a low IS (0.10) B. Acigraph from participant B with a high IS (0.70).

2.3.2.1 Hierarchical regression models

Hierarchical regression models testing associations with cognitive factors including demographic variables (step one), sleep and activity variables (step two), health factors (step three), and non-parametric variables (step four) were constructed. All models for each step were significant at p< 0.0001. R^2 and ΔR^2 for each step for each hierarchical regression model predicting the cognitive factors are listed in Table 7. For each model, step one predicted a significant amount of variance in the cognitive factors, indicating that age, gender, race, ethnicity, and years of education accounted for a significant amount of variance in each model. Neither step two nor three added significantly to R^2.

Similar to extended cosine models, the WASO coefficient was the only additional coefficient that remained significant above and beyond demographic variables at each step in the visuospatial reasoning (step two: β = -0.09, p = 0.02 ;step three: β = -0.09, p = 0.03), processing speed (step two: β = -0.09, p = 0.03;step three: β = -0.09 p = 0.03), working memory (step two: β = -0.09, p = 0.03 ;step three: β = -0.09, p = 0.03), and executive functioning (step three: β = -0.08, $p < 0.05$; step two: β = -0.08, $p < 0.05$) models. Again WASO, when added to the model in step two, was significantly related to all primary cognitive domains.

Primary domains: visuospatial reasoning, processing speed, executive functioning, working memory. Table 9 reports model summary statistics and coefficients for step four of each cognitive factor model. IS and IV coefficients were not significant in the visuospatial reasoning, processing speed, executive functioning, working memory models. Again, WASO was significant in the visuospatial reasoning (β = -0.08, p = 0.03), processing speed (β = - 0.09, p = 0.03), working memory (-0.09, p = 0.03), and executive functioning (β =-0.08, p = 0.04) models.

Secondary domains: verbal proficiency and verbal learning. IS and IV coefficients were not significant in step four of the verbal learning models (Table 9). Consistent with correlation analyses, IV was significantly correlated with verbal proficiency above and beyond other covariates (β = 0.11, p = 0.010, $F_{(14,401)}$ = 22.28, R^2 = 0.45, p < 0.0001; Figure 4B) and the fourth step of the model added a significant amount of variance above and beyond the other steps in the model (ΔR^2 = 0.02, p = 0.03). This unexpected association was further investigated in *post hoc* analyses (pg. 40). Importantly, the association between IV and verbal proficiency does not survive correction for the six non-parametric models completed (corrected p-value = 0.009) in the sample and therefore the association should be considered preliminary and interpreted with caution.

Table 9. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Nonparametric Analyses For Cognitive Factors

Variable	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.03 (-0.21)*** 0.01	-0.03 (-0.24)*** 0.01	-0.02 (-0.18)*** 0.01	-0.03 (-0.23)*** 0.01	-0.03 (-0.22)*** 0.01	0.01 (-0.03) 0.01
Gender	-0.17 (-0.09)* 0.08	-0.13 (-0.07) 0.08	0.08 (0.05) 0.09	-0.06 (-0.04) 0.08	-0.08(-0.05) 0.08	-0.10 (-0.06) 0.07
Race	-0.91 (-0.37)*** 0.10	-0.90 (-0.37)*** 0.11	-0.69 (-0.29)*** 0.11	-0.88(-0.38)*** 0.10	-0.90 (-0.38)*** 0.10	-0.80 (-0.34)*** 0.10
Testing Time	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.05) <0.01
Years of School	0.08 (0.25)*** 0.01	0.07 (0.21)*** 0.02	0.08 (0.24)*** 0.02	0.07 (0.21)*** 0.01	-0.04 (0.21)*** 0.01	0.12 (0.39)*** 0.01
Employment Status	-0.04 (-0.01) 0.12	0.03 (0.01) 0.12	0.04 (0.01) 0.13	-0.04 (-0.01) 0.12	-0.04 (-0.01) 0.12	-0.18 (-0.06) 0.11
Weekly Activity	0.06 (0.02) 0.10	0.09 (0.04) 0.11	-0.04(-0.02) 0.11	0.08 (0.03) 0.10	0.11 (0.05) 0.10	-0.01 (-0.01) 0.10
WASO	-0.01 (-0.09)* 0.01	-0.01 (-0.09)* 0.01	-0.01(-0.04) 0.01	-0.01 (-0.08)* 0.01	-0.01 (-0.09)* 0.01	-0.01 (-0.05) 0.01
TST	<0.01 (0.01) <0.01	<0.01 (0.01) <0.01	<0.01 (0.03) <0.01	<0.01 (0.02) <0.01	<0.01 (0.02) <0.01	<0.01 (-0.02) <0.01
BMI	-0.01 (-0.05) 0.01	-0.01 (-0.02) 0.01	-0.01 (-0.01) 0.01	-0.01 (-0.03) 0.01	0.01 (-0.02) 0.01	-0.01 (-0.05) 0.01
Smoking Status	-0.05(-0.04) 0.05	-0.01 (-0.01) 0.06	-0.08 (-0.07) 0.06	-0.01 (-0.01) 0.05	0.01 (0.01) 0.05	-0.09 (-0.07) 0.05
Weekly Alcohol	0.01 (0.04) 0.01	0.01 (0.06) 0.01	0.02 (0.09) 0.01	0.01 (0.07) 0.01	0.01 (0.06) 0.01	0.01 (0.05) 0.01
IS	0.03 (0.01) 0.23	0.01 (0.01) 0.24	0.02 (0.01) 0.25	0.01 (0.01) 0.23	-0.02 (0.01) 0.23	0.03 (0.01) 0.22
IV	0.14 (0.03) 0.19	0.09 (0.02) 0.20	0.38 (0.09) 0.21	0.13 (0.03) 0.19	0.15 (0.03) 0.19	0.47 (0.11)** 0.18

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.001$) BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset, IV= intradaily variability, IS = interdaily stability *** $p<0.001$, ** $p< 0.01$, *$p<0.05$

2.3.3 Aim 3: Interaction Analyses

In order to explore a potential interaction between age and amplitude in the association between amplitude and verbal proficiency, an interaction term was included in the model in step five. Consistent with study predictions, the interaction term was not significant (β = -0.27, p = 0.50), though the model was significant ($F_{(15,397)}$ = 21.42, R^2 = 0.46, p < 0.001).

In order to explore a potential interaction between age and IV, an interaction term was included in the model. The interaction term was not significant (β = 0.29, p = 0.26), though the model was significant (R^2 = 0.45, $F_{(15,397)}$ = 20.67, p < 0.001).

2.3.4 Post Hoc Analyses

For these analyses, p < 0.05 was adopted consistent with standard methods for *post hoc* analyses.

2.3.4.1 Analyses stratified by gender

Due to previous findings that circadian associations could differ by gender (e.g., Swanson et al., 2017), and in order to better understand the impact of gender on the current analyses, hierarchical regression models used in the primary analyses were stratified by gender. Regarding the extended cosine measures, analyses in women (n = 214) revealed an association between amplitude and verbal learning performance (β = -0.14, p = 0.02, $F_{(13,213)}$ = 10.68, R^2 = 0.41, p < 0.0001, Table 10) and amplitude with verbal proficiency performance (β = -0.13, $F_{(13,213)}$ = 19.81, p = 0.01, R^2 = 0.56, p < 0.0001, Table 10) above and beyond study covariates. There were no significant associations in the extended cosine measures when restricting to analyses to men only (n = 184, Table 11).

Table 10. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Extended Cosine Analyses For Cognitive Factors Only in Women

Variable	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.03 (-0.23)***	-0.03 (-0.24)***	-0.02 (-0.12)*	-0.03 (-0.24)***	-0.03 (-0.24)***	0.00 (-0.02)
	0.01	0.01	0.01	0.01	0.01	0.01
Race	-1.09 (-0.46)***	-1.08 (-0.46)***	-0.82 (-0.37)***	-1.04 (-0.46)***	-1.05 (-0.46)***	-0.95 (-0.41)***
	0.13	0.14	0.14	0.14	0.14	0.12
Testing Time	<0.01 (0.05)	<0.01 (0.06)	<0.01 (0.08)	<0.01 (0.05)	<0.01 (0.06)	<0.01 (0.10)*
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Years of School	0.10 (0.27)***	0.08 (0.23)***	0.10 (0.29)***	0.08 (0.23)***	0.07 (0.22)***	0.16 (0.44)***
	0.02	0.02	0.02	0.02	0.02	0.02
Employment Status	-0.03 (-0.01)	0.02 (0.01)	-0.01 (<0.01)	-0.04 (-0.02)	-0.06 (-0.02)	-0.23 (-0.09)
	0.15	0.15	0.14	0.14	0.14	0.13
Weekly Activity	-0.04 (-0.02)	<0.01 (<0.01)	-0.11 (-0.04)	-0.02 (-0.01)	<0.01 (<0.01)	-0.11 (-0.04)
	0.15	0.16	0.15	0.15	0.15	0.14
WASO	<0.01 (-0.06)	<0.01 (-0.04)	<0.01 (0.02)	<0.01 (-0.06)	<0.01 (-0.06)	-0.01 (-0.10)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
TST	<0.01 (0.03)	<0.01 (0.04)	<0.01 (0.04)	<0.01 (0.04)	<0.01 (0.05)	<0.01 (-0.02)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI	-0.01 (-0.05)	-0.01 (-0.04)	-0.02 (-0.11)	-0.01 (-0.03)	-0.01 (-0.04)	-0.01 (-0.06)
	0.01	0.01	0.01	0.01	0.01	0.01
Smoking Status	-0.12 (-0.09)	-0.07(-0.05)	-0.18 (-0.14)*	-0.05 (-0.04)	-0.05 (-0.04)	-0.17 (-0.13)*
	0.08	0.08	0.08	0.08	0.08	0.07
Weekly Alcohol	0.01 (0.05)	0.02 (0.08)	0.03 (0.14)*	0.02 (0.07)	0.02 (0.07)	0.01(0.06)
	0.01	0.01	0.01	0.01	0.01	0.01
Amplitude	-0.18 (-0.10)	-0.17 (-0.09)	-0.25 (-0.14)*	-0.11 (-0.06)	-0.11(-0.07)	-0.23(-0.13)*
	0.10	0.11	0.10	0.10	0.10	0.09
Acrophase	0.07 (0.07)	0.07 (0.07)	0.05 (0.05)	0.06 (0.06)	0.07 (0.07)	0.06 (0.06)
	0.05	0.06	0.05	0.05	0.05	0.05
ΔR^2	0.01	0.01	0.02*	0.006	0.008	0.016*

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.001$). BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset *** $p<0.001$, ** $p< 0.01$, *$p<0.05$

Table 11. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Extended Cosine Analyses For Cognitive Factors Only in Men

Variables	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.02 (-0.19)**	-0.03 (-0.23)**	-0.03 (-0.26)**	-0.02 (-0.21)**	-0.02 (-0.20) **	<0.01 (-0.03)
	0.01	0.01	0.01	0.01	0.01	0.01
Race	-0.71 (-0.30)***	-0.69 (-0.29)***	-0.55 (-0.22)**	-0.71 (-0.30)***	-0.75 (-0.32)***	-0.69 (-0.30)***
	0.17	0.18	0.20	0.17	0.17	0.17
Testing Time	<0.01 (-0.03)	<0.01(-0.09)	<0.01 (-0.07)	<0.01(-0.08)	<0.01 (-0.06)	<0.01 (<0.01)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Years of School	0.07 (0.26)***	0.06 (0.21)**	0.07 (0.23)**	0.06 (0.23)**	0.07 (0.24)**	0.11 (0.39)***
	0.02	0.02	0.02	0.02	0.02	0.02
Employment Status	-0.20 (-0.06)	-0.07 (-0.02)	<0.01 (<0.01)	-0.13(-0.04)	-0.10 (-0.03)	-0.32 (-0.10)
	0.22	0.23	0.26	0.23	0.23	0.22
Weekly Activity	0.21(0.09)	0.26 (0.11)	0.14 (0.06)	0.22 (0.10)	0.27 (0.12)	0.18 (0.08)
	0.15	0.16	0.18	0.16	0.16	0.15
WASO	-0.01 (-0.15)*	-0.01 (-0.17)*	-0.01 (-0.11)	-0.01 (-0.14)	-0.01 (-0.16)*	<0.01 (-0.03)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
TST	<0.01 (-0.08)	<0.01 (-0.08)	<0.01(-0.01)	<0.01 (-0.05)	<0.01 (-0.06)	<0.01 (-0.04)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI	-0.01 (-0.08)	<0.01 (-0.01)	0.02(0.11)	-0.01 (-0.03)	<0.01 (0.02)	<0.01 (-0.02)
	0.01	0.01	0.02	0.01	0.01	0.01
Smoking Status	<0.01 (<0.01)	0.03(0.03)	-0.02 (-0.02)	0.01 (0.01)	0.02 (0.02)	-0.03 (-0.03)
	0.07	0.08	0.09	0.08	0.08	0.07
Weekly Alcohol	0.01 (0.04)0.01	0.01(0.05)	0.01(0.05)	0.01 (0.08)	0.01 (0.06)	0.01 (0.03)
		0.01	0.01	0.01	0.01	0.01
Amplitude	-0.05 (-0.04)	-0.04(-0.03)	0.05 (0.03)	-0.09 (-0.06)	-0.09 (-0.06)	-0.10 (-0.07)
	0.10	0.11	0.12	0.10	0.10	0.10
Acrophase	0.03 (0.04)	<0.01 (<0.01)	0.01(0.02)	0.01 (0.01)	0.02 (0.02)	0.09 (0.12)
	0.05	0.06	0.06	0.05	0.05	0.05
ΔR^2	0.002	0.001	0.001	0.003	0.004	0.016

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant (p<0.001). BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset, IV= intradaily variability, IS = interdaily stability *** p <0.001, ** p< 0.01, *p<0.05

In contrast, associations were found in men but not in women using nonparametric measures. No significant associations were found above and beyond study covariates among women (n = 217, Table 12), though it should be noted that association between IV and verbal proficiency was not significant, but in the same direction as findings reported above for the whole sample (β = 0.09, p = 0.08, $F_{(13,216)}$ = 18.59, R^2 = 0.54, p < 0.0001). Among men (n =185), higher IV was significantly associated with verbal proficiency (β = 0.16, p = 0.04, $F_{(13,184)}$ = 6.31, R^2 = 0.32, p < 0.0001, Table 13) above and beyond study covariates.

Table 12. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Nonparametric Analyses For Cognitive Factors Only in Women

Variables	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.03 (-0.24)***	-0.03 (-0.25)***	-0.02 (-0.12)*	-0.03 (-0.26)***	-0.03 (-0.25)***	<0.01 (-0.03)
	0.01	0.01	0.01	0.01	0.01	0.01
Race	-1.07 (-0.45)***	-1.07 (-0.45)***	-0.81 (-0.36)***	-1.03 (-0.45)***	-1.03 (-0.45)***	-0.96 (-0.41)***
	0.14	0.14	0.14	0.14	0.14	0.13
Testing Time	<0.01 (0.06)	<0.01 (0.06)	<0.01 (0.09)	<0.01 (0.06)	<0.01 (0.07)	<0.01 (0.10)*
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Years of School	0.10 (0.28) ***	0.09 (0.24)***	0.10 (0.29)***	0.08 (0.23)***	0.08 (0.22)***	0.16 (0.44)**
	0.02	0.02	0.02	0.02	0.02	0.02
Employment Status	<0.01 (<0.01)	0.06 (0.02)	0.03 (0.01)	-0.01 (-0.01)	-0.03 (-0.01)	-0.19 (-0.07)
	0.15	0.15	0.14	0.14	0.14	0.13
Weekly Activity	-0.10 (-0.04)	-0.06 (-0.02)	-0.18 (-0.07)	-0.05 (-0.02)	-0.03 (0.01)	-0.19 (-0.07)
	0.15	0.15	0.15	0.15	0.15	0.14
WASO	<0.01 (-0.05)	<0.01 (-0.03)	<0.01 (0.05)	<0.01 (-0.05)	<0.01 (-0.05)	<0.01(-0.07)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
TST	<0.01 (0.04)	<0.01 (0.05)	<0.01 (0.05)	<0.01 (0.05)	<0.01 (0.05)	<0.01 (<0.01)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI	-0.01 (-0.03)	-0.01 (-0.03)	-0.01(-0.08)	<0.01 (-0.02)	-0.01 (-0.03)	-0.01 (-0.05)
	0.01	0.01	0.01	0.01	0.01	0.01
Smoking Status	-0.10 (-0.07)	-0.06(-0.04)	-0.18 (-0.14)*	-0.03 (-0.03)	-0.03 (-0.02)	-0.15 (-0.11)*
	0.08	0.08	0.08	0.08	0.08	0.07
Weekly Alcohol	0.01 (0.05)	0.02 (0.08)	0.03 (0.14)*	0.02 (0.07)	0.02 (0.07)	0.01 (0.05)
	0.01	0.01	0.01	0.01	0.01	0.01
IS	0.11 (0.02)	0.17 (0.03)	0.24 (0.05)	0.10 (0.02)	0.11 (0.02)	-0.04 (-0.01)
	0.30	0.31	0.30	0.29	0.29	0.27
IV	0.24 (0.05)	0.22 (0.04)	0.46 (0.10)	0.17 (0.04)	0.17 (0.04)	0.44 (0.09)
	0.28	0.28	0.27	0.27	0.27	0.25
ΔR^2	0.002	0.002	0.009	0.001	0.001	0.008

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.001$). BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset, IV= intradaily variability, IS = interdaily stability *** $p<0.001$, ** $p< 0.01$, *$p<0.05$

Table 13. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Nonparametric Analyses For Cognitive Factors Only in Men

Variable	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.02 (-0.19)**	-0.03 (-0.23)**	-0.03 (-0.27)***	-0.02 (-0.21)**	-0.02 (-0.20)**	-0.01 (-0.04)
	0.01	0.01	0.01	0.01	0.01	0.01
Race	-0.68 (-0.29)***	-0.68 (-0.28)***	-0.58 (-0.22)**	-0.68 (-0.29)***	-0.72 (-0.30)***	-0.61 (-0.26)***
	0.17	0.17	0.19	0.17	0.17	0.16
Testing Time	<0.01 (-0.02)	<0.01 (-0.09)	<0.01 (-0.08)	<0.01 (-0.08)	<0.01 (-0.06)	<0.01 (0.02)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Years of School	0.07 (0.25)**	0.06 (0.21)**	0.06 (0.19)*	0.06 (0.22)**	0.07 (0.23)**	0.10 (0.35)***
	0.02	0.02	0.02	0.02	0.02	0.02
Employment Status	-0.17 (-0.05)	-0.07 (-0.02)	0.05 (0.01)	-0.10 (-0.03)	0.07 (-0.02)	-0.19 (-0.06)
	0.22	0.23	0.25	0.22	0.22	0.21
Weekly Activity	0.20 (0.09)	0.26 (0.11)	0.15 (0.06)	0.22 (0.10)	0.26 (0.11)	0.15 (0.07)
	0.15	0.16	0.17	0.15	0.15	0.14
WASO	-0.01 (-0.15)*	-0.01 (-0.17)*	-0.01 (-0.13)	-0.01 (-0.13)	-0.01 (-0.14)*	<0.01 (-0.02)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
TST	<0.01 (-0.08)	<0.01 (-0.09)	<0.01 (-0.03)	<0.01 (-0.05)	<0.01 (-0.06)	<0.01 (-0.04)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI	-0.02 (-0.08)	<0.01 (-0.01)	0.02 (0.09)	-0.01 (-0.03)	<0.01 (0.01)	-0.01 (-0.04)
	0.01	0.01	0.02	0.01	0.01	0.01
Smoking Status	0.01 (0.01)	0.04(0.03)	<0.01 (<0.01)	0.02 (0.02)	0.02 (0.02)	-0.01 (-0.01)
	0.07	0.08	0.09	0.08	0.08	0.07
Weekly Alcohol	0.01 (0.04)	0.01(0.05)	0.01 (0.06)	0.01 (0.08)	0.01 (0.07)	0.01 (0.04)
	0.01	0.01	0.01	0.01	0.01	0.01
IS	0.13 (0.02)	0.01(<0.01)	0.01 (<0.01)	0.04 (0.01)	-0.06 (-0.01)	0.35 (0.07)
	0.38	0.40	0.22	0.39	0.39	0.37
IV	0.16 (0.04)	0.14 (0.04)	0.49 (0.12)	0.20 (0.05)	0.23 (0.06)	0.57 (0.16)*
	0.28	0.29	0.32	0.28	0.28	0.27
ΔR^2	0.001	0.001	0.012	0.002	0.004	0.018

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.001$). BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset, IV= intradaily variability, IS = interdaily stability *** $p<0.001$, ** $p< 0.01$, *$p<0.05$

2.3.4.2 Impact of race

Due to changes in the original covariates included in the models from not including race to including race in the final model, it was clear that race had a large impact on the results. In order to better understand how race was impacting the final analyses, race was excluded from both extended cosine and nonparametric hierarchical regression models. Regarding extended cosine models, there were major differences in the amplitude verbal proficiency associations such that including race as a covariate lead to a significant association between amplitude and verbal proficiency, while not including race in the model meant that the amplitude coefficient was no longer significant (see Table 14, β = -0.07, p = 0.10, $F_{(13,397)}$ = 16.18, R^2 = 0.35, p < 0.0001). No other differences were found relative to the primary analyses. No significant differences were found in the relationship between nonparametric RAR measures and cognitive factors (see Table 15), as IV remains significantly associated with verbal proficiency above and beyond study covariates in both models including and excluding race (β = 0.09, p = 0.049, $F_{(13,397)}$ = 16.21, R^2 = 0.35, p < 0.0001).

Table 14. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Extended Cosine Analyses For Cognitive Factors Excluding Race Covariates

Variable	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.03 (-0.23)***	-0.03 (-0.25)***	-0.02 (-0.19)***	-0.03 (-0.24)***	-0.03 (-0.23)***	-0.01 (-0.04)
	0.01	0.01	0.01	0.01	0.01	0.01
Gender	-0.20 (-0.11)*	-0.16 (-0.09)	0.04 (0.02)	-0.10 (-0.05)	-0.12 (-0.07)	-0.13 (-0.07)
	0.09	0.09	0.09	0.09	0.09	0.08
Testing Time	<0.01 (-0.01)	<0.01 (-0.04)	<<0.01 (-0.02)	<0.01 (-0.05)	<0.01 (-0.03)	<0.01 (0.03)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Years of School	0.10 (0.31)***	0.08 (0.26)***	0.09 (0.29)***	0.08 (0.27)***	0.08 (0.27)***	0.14 (0.46)***
	0.02	0.02	0.02	0.02	0.02	0.01
Employment Status	-0.19 (-0.06)	-0.11 (-0.04)	-0.07 (-0.03)	-0.17 (-0.06)	-0.18 (-0.06)	-0.34 (-0.12)**
	0.13	0.13	0.13	0.13	0.13	0.12
Weekly Activity	0.21 (0.08)	0.23 (0.09)*	0.04 (0.02)	0.21 (0.09)	0.25 (0.10)*	0.14 (0.06)
	0.11	0.12	0.12	0.11	0.11	0.11
WASO	-0.01 (-0.13)**	-0.01 (-0.12)**	0.01 (-0.06)	-0.01 (-0.11)**	-0.01 (-0.12)**	-0.01 (-0.10)*
	0.01	0.01	0.01	0.01	0.01	0.01
TST	<0.01 (0.05)	<0.01 (0.06)	<0.01 (0.07)	<0.01 (-0.11)	<0.01 (0.07)	<0.01 (0.03)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI	-0.02 (-0.10)	-0.01 (-0.07)	-0.01 (0.04)	-0.01(-0.07)	-0.01 (-0.06)	-0.02 (-0.09)
	0.01	0.01	0.01	0.01	0.01	0.01
Smoking Status	-0.08(-0.06)	-0.04 (-0.03)	-0.12 (-0.10)*	-0.04 (-0.03)	-0.03 (-0.03)	-0.13 (-0.11)*
	0.06	0.06	0.06	0.06	0.06	0.05
Weekly Alcohol	0.02 (0.09)*	0.02 (0.10)*	0.03(0.12)**	0.02 (0.12)**	0.02 (0.11)*	0.02 (0.09)*
	0.01	0.01	0.01	0.01	0.01	0.01
Amplitude	-0.06 (-0.03)	-0.04 (-0.02)	-0.02 (-0.01)	-0.04 (-0.02)	-0.04 (-0.02)	-0.12 (-0.07)
	0.08	0.08	0.08	0.08	0.08	0.07
Acrophase	0.01 (0.01)	-0.02 (-0.02)	-0.02 (-0.02)	-0.01 (-0.01)	<0.01 (0.01)	0.03 (0.04)
	0.04	0.04	0.04	0.04	0.04	0.04
ΔR^2	0.001	0.001	<0.001	0.001	<0.001	0.006

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.001$). BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset. *** $p<0.001$, ** $p< 0.01$, *$p<0.05$

Table 15. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Nonparametric Analyses For Cognitive Factors Excluding Race Covariate

Variable	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.03 (-0.22)***	-0.03 (-0.25)***	-0.02 (-0.19)***	-0.03 (-0.24)***	-0.03 (-0.24)***	-0.01 (-0.4)
	0.01	0.01	0.01	0.01	0.01	0.01
Gender	-0.22 (-0.12)**	-0.17 (-0.09)	0.05 (0.03)	-0.10(-0.06)	-0.12 (-0.07)	-0.14(-0.08)
	0.09	0.09	0.09	0.09	0.09	0.08
Testing Time	<0.01 (-0.01)	<0.01 (-0.04)	<0.01 (-0.02)	<0.01(-0.04)	<0.01 (-0.02)	<0.01 (0.03)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Years of School	0.10 (0.31)***	0.09 (0.26)***	0.09 (0.28)***	0.09 (0.27)***	0.09 (0.27)***	0.14 (0.44)***
	0.02	0.02	0.02	0.02	0.02	0.01
Employment Status	-0.18 (-0.06)	-0.11 (-0.04)	-0.07 (-0.02)	-0.17 (-0.06)	-0.17 (-0.06)	-0.30 (-0.10)*
	0.13	0.13	0.13	0.13	0.13	0.12
Weekly Activity	0.19 (0.08)	0.22 0.09)	0.06 (0.02)	0.21 (0.09)	0.24 (0.10)*	0.10 (0.04)
	0.11	0.12	0.12	0.11	0.11	0.10
WASO	-0.01 (-0.12)**	-0.01 (-0.12)**	<0.01 (-0.06)	-0.01 (-0.11)**	-0.01 (-0.12)**	<0.01 (-0.08)
	0.01	0.01	0.01	0.01	0.01	0.01
TST	<0.01 (0.05)	<0.01 (0.06)	<0.01 (0.07)	<0.01 (0.07)	<0.01 (0.07)	<0.01 (0.03)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI	-0.02 (-0.09)*	-0.01 (-0.06)	-0.01 (-0.06)	-0.01 (-0.07)	-0.01 (-0.06)	-0.02 (-0.09)
	0.01	0.01	0.01	0.01	0.01	0.01
Smoking Status	-0.08 (-0.06)	-0.04 (-0.03)	-0.11 (-0.04)	-0.04 (-0.03)	-0.03 (-0.03)	-0.12 (-0.10)*
	0.06	0.06	0.01	0.06	0.06	0.05
Weekly Alcohol	0.02 (0.09)	0.02 (0.10)*	0.03 (0.12)**	0.02 (0.12)**	0.02 (0.11)*	0.02 (0.09)*
	0.01	0.01	0.01	0.01	0.01	0.01
IS	0.25 (0.04	0.20 (0.04)	0.17 (0.03)	0.20 (0.04)	0.18 (0.03)	0.22 (0.04)
	0.25	0.26	0.26	0.25	0.25	0.23
IV	0.04 (0.01)	0.01 (0.01)	0.32 (0.07)	0.05 (0.01)	0.07 (0.02)	0.39 (0.09)*
	0.21	0.22	0.22	0.12	0.21	0.20
ΔR^2	0.002	0.001	0.005	0.001	0.001	0.007

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.001$). BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset, IV= intradaily variability, IS = interdaily stability *** $p<0.001$, ** $p< 0.01$, *$p<0.05$

2.3.4.3 Subtest analyses

Although the cognitive domains confirmed by CFA were originally hypothesized to be associated with RARs, previous literature supports associations with single subtests (e.g., Luik et al., 2015; Walsh et al., 2014). Therefore, post-hoc analyses with individual cognitive subtests were conducted. In order to limit the number of subtest models completed in the study, *post hoc* analyses were limited to subtests that have consistently been associated with RARs in the older adult literature, and were investigated in order to be able compare results in the current middle-aged sample. A review of the literature revealed that Trail Making Test A & B and the Stroop task were consistently included RAR analyses and were significantly associated with both extended cosine (Walsh et al., 2014) and nonparametric measures (Lim et al., 2009; Oosterman et al.,2012; Luik et al., 2015). Therefore, Trail Making Test A, the differences between Trail Making Test A and B, Stroop Color, Stroop Word, Stroop Color-Word, and the interference score were analyzed. As with primary analyses, scores were winsorized and transformed if skewed. Due to skew, Trails Making Task A and the difference between Trails Making Task B and A were log transformed. Pearson's correlations were calculated between individual test scores, rhythm measures, and study covariates. Similar four step hierarchical models were created as in the main analyses. If there was a significant effect of the RAR measures, an interaction term was explored in the fifth step.

Correlations. Correlations between study covariates and selected subtests are listed in Table 16. Correlations between both the extended cosine and non-parametric rest/activity rhythm measures and subtests are summarized in Table 17. Within the extended cosine measures, amplitude was significantly correlated with Trail Making Test A such that lower amplitude was

associated with longer time to complete Trail Making Test A (r = -0.11, p = 0.03). Earlier acrophase was significantly associated with more words said on the color portion of the Stroop task (r =-0.10, p = 0.04) and more interference on the Stroop task (r = 0.11, p = 0.03).

Table 16. Correlations Between Study Covariates and Selected Subtests

Variable	Trails A	Trails Difference	Stroop Color	Stroop Word	Stroop Color Word	Stroop Interference
Age	0.12**	0.12**	-0.10	-0.07	-0.27**	-0.26**
Gender	-0.03	0.02	0.09	0.05	-0.02	-0.11*
Race	0.27**	0.22**	-0.14**	-0.14**	-0.30**	-0.25**
Testing Time	0.05	0.02	0.06	0.07	-0.05	-0.13*
Years of School	-0.05	-0.19**	0.04	0.13**	0.14**	0.11*
Employment Status	-0.03	0.07	0.00	0.02	-0.07	-0.11*
Weekly Activity	-0.11*	-0.08	0.03	0.06	0.05	0.03
WASO	0.06	0.07	-0.10	-0.05	-0.13**	-0.10
TST	-0.06	-.11*	0.03	0.02	0.06	0.05
BMI	0.03	0.07	-0.04	-0.04	-0.12*	-0.11*
Smoking Status	0.10*	0.08	-0.08	-0.07	-0.05	0.01
Weekly Alcohol	-0.01	-0.05	0.08	0.06	0.12*	0.08

Note. WASO = wake after sleep onset, TST = total sleep time, BMI = body mass index ** $p<0.01$, *$p<0.05$

Table 17. Correlations Between RAR and Subtests

Subtest	Amplitude	Acrophase	IS	IV
Stroop Color	0.07	-0.10*	0.01	0.07
Stroop Word	0.07	-0.03	0.01	0.09
Stroop Color Word	0.06	0.03	0.10*	0.05
Stroop Interference	0.01	0.11*	0.12*	-0.02
Trails Difference	-0.03	0.02	0.08	-0.06
Trails A	-0.11*	0.07	-0.04	0.03

Note. IV= intradaily variability, IS = interdaily stability ** $p<0.01$, *$p<0.05$

Several additional significant correlations were found when investigating the associations between non-parametric RAR measures and subtests. For example, more stability in rhythms (higher IS) was significantly associated with more words on the color-word portion of the Stroop task ($r = 0.10$, $p = 0.04$) and less interference on the Stroop task ($r = 0.10$, $p = 0.02$).

Hierarchical regression models. Extended cosine models were created for each of the selected subtests. In regard to the Stroop Color task, the fourth step was significant ($F_{(14,397)} = 2.21$, $R^2 = 0.08$, $p = 0.002$) and acrophase remained significantly associated with performance above and beyond study covariates ($\beta = -0.11$, $p = 0.04$, Table 18). However, the fourth step, which entered both acrophase and amplitude, did not significantly add to the variance explained by the covariates ($\Delta R^2 = 0.01$, $p = 0.11$), likely due to the non-significant contribution of amplitude to the model. An interaction term between acrophase and age was included in the model and was not significant ($\beta = -0.19$, $p = 0.79$). Although remaining analyses revealed significant models for each step, neither amplitude nor acrophase were significantly associated with Trial Making Test A, the different between Trail Making Test A and B, Stroop Word, Stroop Color Word, nor the interference score (see Table 18).

Table 18. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Extended Cosine Measures for Selected Subtests

Variable	Trails A	Trails Difference	Stroop Color	Stroop Color Word	Stroop Interference
Age	0.01 (0.19)***	<0.01 (0.10)	-0.20 (-0.12)*	-0.32 (-0.25)***	-0.23 (-0.22)***
	0.00	<0.01	0.09	0.07	0.05
Gender	-0.02 (-0.08)	-0.01 (-0.03)	2.96 (0.12)*	1.28 (0.07)	-0.41(-0.03)
	0.01	0.02	1.32	0.98	0.77
Testing Time	<0.01 (0.00)	0.09 (0.15)	<0.01 (0.09)	<0.01 (-0.02)	<0.00 (-0.10)
	<0.01	0.03	<0.01	<0.01	<0.01
Race	0.08 (0.25)***	<0.01 (-0.01)**	-3.70 (-0.12)*	-6.13 (-0.25)***	-4.03 (-0.21)***
	0.02	<0.01	1.74	1.29	1.02
Years of School	<0.01 (0.01)	-0.01 (-0.15)**	0.03 (0.01)	0.24 (0.07)	0.11 (0.04)
	<0.01	<0.01	0.23	0.17	0.13
Employment Status	-0.03 (-0.07)	0.04 (0.05)	1.21 (0.03)	-1.05 (-0.03)	-1.89 (-0.08)
	0.02	0.04	1.98	1.46	1.16
Weekly Activity	-0.02 (-0.06)	-0.03 (-0.05)	0.08 (0.00)	0.10 (<0.01)	-0.09 (0.00)
	0.02	0.03	1.74	1.29	1.02
WASO	0.00 (0.00)	<0.01 (0.03)	-0.05 (-0.07)	-0.04 (-0.08)	-0.02 (-0.05)
	0.00	<0.01	0.03	0.03	0.02
TST	0.00 (0.01)	<0.01 (-0.08)	-0.01 (-0.02)	<0.01 (<0.01)	0.00 (0.02)
	0.00	<0.01	0.01	0.01	0.01
BMI	0.00 (-0.07)	<0.01 (-0.03)	0.06 (0.03)	-0.02 (-0.01)	-0.06 (-0.04)
	0.00	<0.01	0.13	0.09	0.07
Smoking Status	0.01 (0.04)	<0.01 (<0.01)	-1.01 (-0.06)	0.21 (0.02)	0.69 (0.07)
	0.01	0.02	0.87	0.64	0.51
Weekly Alcohol	0.00 (-0.01)	<0.01 (-0.04)	0.27 (0.10)	0.24 (0.11)	0.09 (0.05)
	0.00	<0.01	0.14	0.11	0.08
Amplitude	-0.01 (-0.04)	<0.01 (<0.01)	0.52 (0.02)	-0.58 (-0.03)	-0.96 (-0.07)
	0.01	0.02	1.18	0.88	0.69
Acrophase	0.01 (0.07)	<0.01 (<0.01)	-1.25 (-0.11)*	0.18 (0.02)	0.70 (0.10)
	0.01	0.01	0.61	0.45	0.36
ΔR^2	0.006	<0.001	0.01	0.01	0.01

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.01$). Stroop word not included because fourth step model was not significant. BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset.*** $p<0.001$, ** $p< 0.01$, *$p<0.05$

Table 19. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Nonparametric Measures for Selected Subtests

Variable	Trails A	Trails Difference	Stroop Word	Stroop Color	Stroop Color Word	Stroop Interference
Age	0.00 (0.19)***	0.00 (0.10)*	-0.18 (-0.07)	-0.18 (-0.11)*	-0.33 (-0.25)***	-0.24 (-0.23)***
	0.00	0.00	0.13	0.09	0.06	0.05
Gender	-0.02 (-0.08)	-0.02 (-0.05)	3.94 (0.11)*	3.55 (0.15)**	1.19 (0.06)	-0.84 (-0.06)
	0.01	0.02	1.98	1.31	0.96	0.76
Testing Time	-0.02 (-0.06)	0.00 (-0.01)	0.00 (0.08)	0.00 (0.07)	0.00 (0.00)	0.00 (-0.07)
	0.02	0.00	0.00	0.00	0.00	0.00
Years of School	0.00 (0.01)	-0.01 (-0.14)**	0.58 (0.09)	-0.06 (-0.01)	0.21(0.06)	0.14 (0.05)
	0.00	0.00	0.35	0.23	0.17	0.14
Employment Status	0.00 (0.01)	0.04 (0.06)	2.21 (0.04)	0.83 (0.02)	-0.68 (-0.02)	-1.39 (-0.06)
	0.00	0.04	2.97	1.96	1.44	1.15
Race	0.08 (0.26)***	0.10 (0.17)**	-6.09 (-0.13)*	-4.27 (-0.13)*	-5.81 (-0.23)***	-3.41 (-0.17)**
	0.02	0.03	2.62	1.73	1.28	1.01
Weekly Activity	-0.02 (-0.07)	-0.03 (-0.05)	1.87 (0.04)	0.64 (0.02)	0.06 (0.00)	-0.45 (-0.02)
	0.02	0.03	2.59	1.71	1.26	1.00
WASO	0.00 (0.01)	0.00 (0.03)	-0.03 (-0.03)	-0.05 (-0.08)	-0.04 (-0.07)	-0.01 (-0.03)
	0.00	0.00	0.05	0.03	0.02	0.02
TST	0.00 (0.00)	0.00 (-0.07)	-0.01 (-0.03)	-0.01 (-0.03)	0.00 (0.01)	0.00 (0.02)
	0.00	0.00	0.02	0.01	0.01	0.01
BMI	0.00 (-0.07)	0.00 (-0.03)	0.11 (0.03)	0.06 (0.03)	-0.01 (-0.01)	-0.05 -0.03)
	0.00	0.00	0.19	0.12	0.09	0.07
Smoking Status	0.01 (0.05)	0.00 (<0.01)	-0.31 (-0.01)	-0.85 (-0.05)	0.35 (0.03)	0.70 (0.07)
	0.01	0.02	1.31	0.87	0.64	0.51
Weekly Alcohol	0.00 (-0.01)	0.00 (-0.03)	0.26 (0.06)	0.28 (0.10)	0.27 (0.12)*	0.11 (0.07)
	0.00	0.00	0.22	0.14	0.11	0.09
IS	-0.01 (-0.01)	0.13 (0.10)	3.91 (0.04)	2.19 (0.03)	6.30 (0.11)*	4.71 (0.11)*
	0.04	0.07	5.80	3.83	2.82	2.24
IV	0.01 (0.01)	0.00 (<0.01)	8.54 (0.10)	5.66 (0.10)	3.66 (0.08)	0.29 (0.01)
	0.03	0.06	4.81	3.18	2.34	1.86
ΔR^2	<0.001	0.009	0.008	0.008	0.01	0.01

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. All step four models were significant ($p<0.01$). Stroop word not included because fourth step model was not significant. BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset, IV= intradaily variability, IS = interdaily stability *** $p<0.001$, ** $p< 0.01$, *$p<0.05$

Regarding the nonparametric measures, models predicting the Color-Word task and the Stroop interference score were significantly associated with IV and IS. First, the model predicting Color-Word was significant ($F_{(13, 401)} = 6.23$, $R^2 = 0.18$, $p < 0.0001$) although the variance explained by the fourth step of the model was not significant ($\Delta R^2 = 0.01$, $p = 0.05$). IS was significantly associated with the amount of words said in 45 seconds on the Color-Word portion of the Stroop task above and beyond study covariates ($\beta = 0.11$, $p = 0.03$, Table 19). An interaction term entered into a fifth step was not significant ($\beta = -0.45$, $p = 0.15$). Second, the model predicting Stroop interference score was also significant ($F_{(13, 401)} = 5.11$, $R^2 = 0.16$, $p < 0.0001$) though the variance explained by the fourth step of the model was not significant ($\Delta R^2 = 0.01$, $p = 0.10$). The IS coefficient was statistically significant, indicating that individuals with more stability had less interference on the Stroop, while controlling for study covariates ($\beta = 0.11$, $p = 0.04$, Table 19). The interaction term entered in a fifth step was not significant ($\beta = -0.11$, $p = 0.74$). No other models exploring nonparametric measures revealed significant correlations between the rhythm measures and cognition above and beyond covariates.

2.3.4.4 Association between job, education and RAR measures

In primary analyses, we found unexpected associations between RAR measures and verbal proficiency. We hypothesized that this association may be due to the common association between job and education and the relationship between verbal proficiency and education. In other words, we hypothesized that individuals with high verbal proficiency may have more years of education, and may be in high-profile jobs that are more likely to be sedentary, making their daytime activity level lower than expected, and more irregular, leading to blunted amplitude, and greater fragmentation. In this way, having sedentary daytime activity influenced by job, could mediate the relationship between RAR measures and verbal proficiency. In order to better

understand this association, job status and years of education and their associations with amplitude and fragmentation were further explored. To explore job, the Hollingshead classification system (Hollingshead, 1975) was used. Hollingshead's system is a tool that aids in organizing jobs into 10 groups with increasing "prestige" from student or unemployed to the highest type of physician/dentist, engineer, lawyer and professor. Please see caption below Figure 7 for exact type description. Job type, education, and verbal proficiency were all significantly correlated with one another (Table 20), such that individuals with higher verbal proficiency had higher education and more prestigious jobs. Further, higher job type was associated with higher education. However, data in the present sample do not allow us to test whether the higher prestige jobs were more likely to be sedentary, as individual job is not recorded for each participant.

Table 20. Correlations Between, Years of School, Verbal Proficiency and Job Type

Measures	Job Type	Years of School	Verbal Proficiency
Job Type	1	.23**	0.31**
Years of School	0.23**	1	0.53**
Verbal Proficiency	0.31**	0.53**	1

Note** $p<0.01$, *$p<0.05$

Given that gender and race greatly impacted the relationship between amplitude and verbal proficiency, the job type distribution was tested across groups due to the hypothesis that the factor influencing the relationship between amplitude and verbal proficiency must also be impacted by race and gender. A chi square comparing job type distribution by gender was significant with men overall having a higher mean job type than men (X^2=33.93, p <0.01, see Figure 7A), with the largest difference between men and women in type six (type includes secretary; men n = 29, 15.7% vs. women n = 61, 28.1%). A second chi square was completed comparing Caucasian vs. non-Caucasian in job type, which supported that there was a significantly different distribution of jobs between groups (X^2=64.65, p <0.001, Figure 7B) with the largest difference in type seven (Caucasian = 103, 31.0% vs. non-Caucasian = 10, 14.3%).

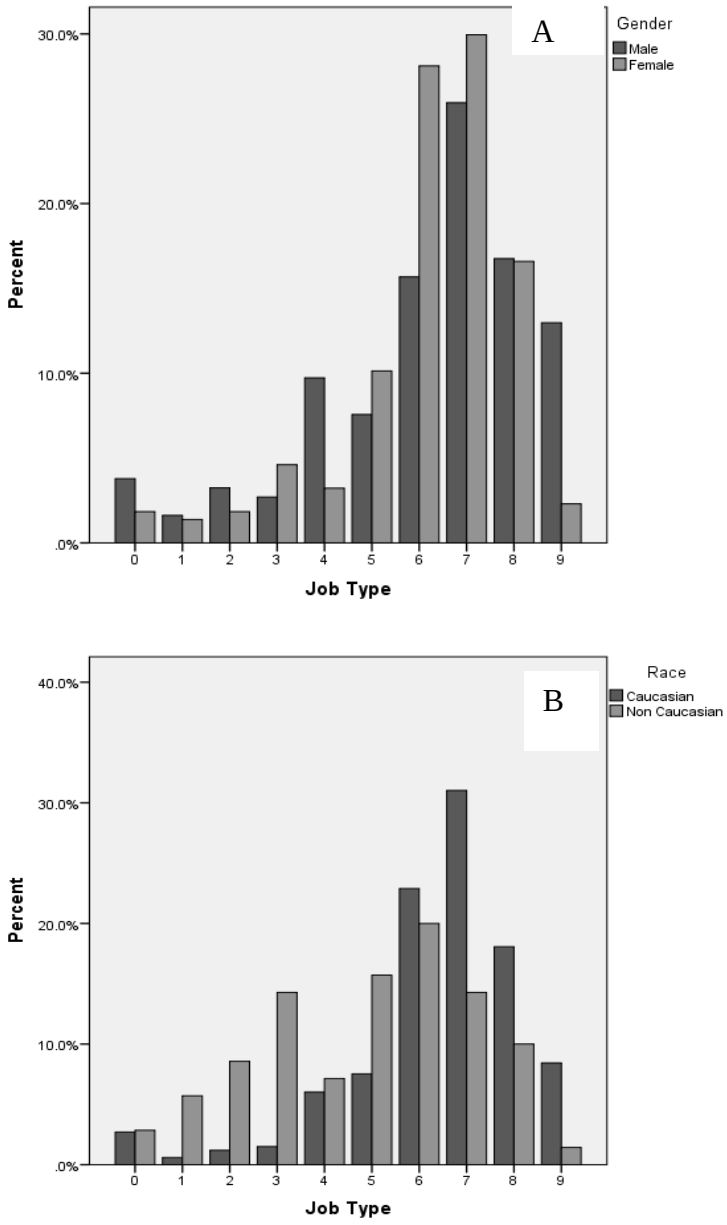

Figure 7. Percentage of Hollingshead job type by gender and race. Type numbers represent the following jobs: 0=student, unemployed, retired over 1 year; 1=unskilled labor, janitorial, welfare, disability; 2=skilled labor, cook, trash collector, waitress/waiter/bartender; 3=steel mill labor, truck driver, miner, assembly line worker, nurse's aide, hairstylist, seamstress; 4=mailman, skilled worker (carpenter, roofer, mechanic, electrician, machinist, bricklayer, welder, baker), sales clerk, secretary; 5=small business owner, bookkeeper, telephone operator, bank teller; 6=police officer, firefighter, store manager, draftsman, secretary; 7=supervisor/department manager, buyer, social worker, teacher, computer programmer, LPN; 8=high school teacher, accountant, pharmacist, clergy, RN; 9=physician/dentist, engineer, lawyer, professor.

To understand if job type may mediate the relationship between RAR amplitude and verbal proficiency, a mediation model using the Process syntax (Hayes, 2012) was built with age, gender, and race as covariates. All pathways were significant (see Figure 8A, a = -0.36, SE = 0.18, p = 0.04; b = 0.08, SE = 0.02, $p < 0.001$; c = -0.19, SE = 0.07, $p < 0.01$) and the indirect effect (c'= -0.03, CI = -0.07- -0.01) was significant but reduced, suggesting job type partially mediated the relationship between amplitude and verbal proficiency. The same mediation model was created to investigate the relationship between fragmentation and verbal proficiency. Again, all pathways were significant (Figure 8B a = 1.45, SE = 0.46, $p < 0.01$; b = 0.08, SE = 0.02, $p < 0.01$; c = 0.83, SE = 0.18, $p < 0.001$). The indirect remained significant effect (c'= 0.11, CI = 0.03 - 0.25) but was reduced indicating job was a partial mediator in the relationship between IV and verbal proficiency.

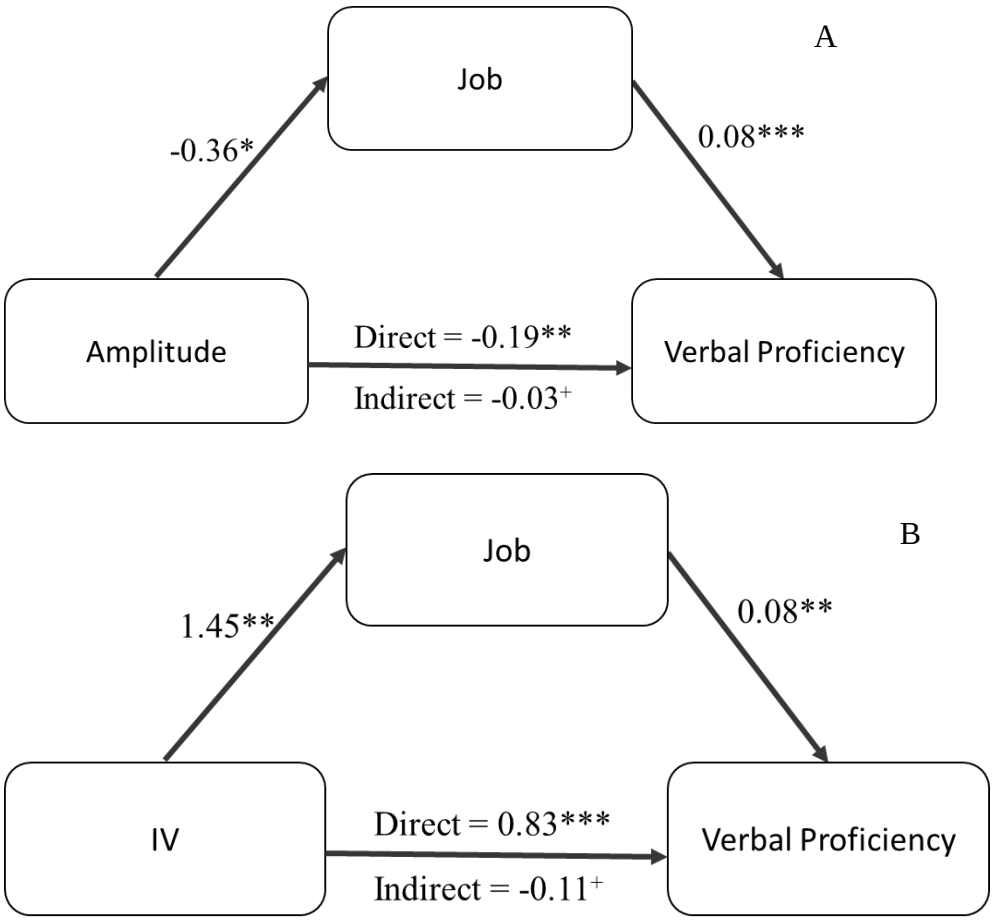

Figure 8. Mediation analyses exploring job as a mediator between RAR amplitude (A) or IV (B). Statistics represent pathway coefficients in models controlling for age, gender, and race. Direct and indirect effects listed. In both cases job type was a partial significant mediator in the relationship between RAR amplitude/IV and verbal proficiency. *p<0.05 **p < 0. 01 ***p<0.001, + represents confidence intervals which do not include 0 (Amplitude indirect effect CI = -0.08 - -0.01; IV indirect effect CI = 0.03 – 0.25)

2.3.4.5 Impact of workday vs. non-workday in analyses

To better understand the potential impact of workday vs. non-workday changes and photoperiod of testing on cognition, correlations between social jetlag, photoperiod, and cognitive factors were explored (Table 21). Social jetlag was measured as the difference between midsleep times between workday and non-workdays and has been previously calculated in the sample (Wong et al., 2015). There were no significant associations between social jetlag or photoperiod and cognitive factors.

2.3.4.6 Duration between actigraphy and assessment

The duration between cognitive testing and actigraphy varied across participants. In order to better understand the impact of time elapsing between actigraphy and testing, sensitivity analyses explored how correlations may differ in those who were tested within 30 days of actigraphy collection compared to those with a longer time between actigraphy and testing. Table 22 includes all relevant correlations. Of note, all correlations remained in the same direction though only verbal proficiency remained significantly correlated with IV when only those with 30 or less days between assessments were included. This is likely due to the closer proximity in time of the WASI testing date to actigraphy collection than the second assessment date, which allowed for a larger group of individuals to be included in analyses for assessments on the WASI date (n =252) relative to the second assessment date (n = 52).

Table 21. Correlations Between Social Jetlag, Photoperiod, and Cognitive Factors.

	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Social Jetlag	-0.02	-0.01	-0.10	0.00	0.00	-0.09
Photoperiod	-0.02	-0.02	-0.04	-0.02	-0.01	0.00

Table 22 Correlations Between RARs and Relevant Cognitive Factors and Subtests Within 30 Days.

Variable	Amplitude	Acrophase	IS	IV
Verbal Proficiency	-0.08	0.04	0.02	0.21**
Stroop Interference	-0.05	0.25	0.10	0.15
Stroop Color	-0.13	-0.18	0.15	0.01
Stroop Color Word	-0.07	0.08	0.17	0.12

Note. ** $p<0.01$, *$p<0.05$ Correlations between previously found associations only looking at those who had actigraphy and testing within 30 days. Because of the different testing days for WASI (vocabulary and verbal proficiency) they have a larger (n=252) compared to the other neuropsychological tests administered on the second date (n=52). Highlighted variables are those that were found to be associated with subtests in the full sample.

2.3.4.7 Additional Covariates.

Additional ancillary analyses that were requested by the committee including additional covariates are included in Appendix C. Including cardiovascular variables did not greatly change results.

2.4 DISCUSSION

Study 1 aimed to explore how RARs, as a proxy for circadian functioning, may be associated with cognition in a healthy middle-aged sample. Specifically, it was hypothesized that RARs would be would be associated with processing speed, executive functioning, working memory, and visuospatial abilities, and that RARs would not be associated with the remaining cognitive domains tested in the sample (i.e., verbal learning and memory and verbal proficiency). Contrary to our predictions, a higher verbal proficiency score was significantly associated with both lower amplitude and higher fragmentation. Both associations were significant after controlling for covariates including demographics, sleep, activity, and health factors. However, only the amplitude association survived correction for multiple tests. Further, although we predicted a significant interaction between RAR measures and age in their relationship with cognitive domains, neither the interaction between fragmentation nor amplitude and age was significant when predicting verbal proficiency. Overall, study hypotheses were not supported, in that no significant associations were found between RARs and the predicted cognitive domains. Instead, an association was demonstrated between RAR higher amplitude and higher verbal proficiency.

2.4.1 Associations with Verbal Proficiency

The relationship between amplitude and verbal proficiency is surprising and inconsistent with the majority of previous literature. Specifically, the current RAR literature in older adults indicates that blunted, delayed, fragmented, and unstable daily RARs are more likely to be associated with (Luik et al., 2015, Oosterman et al, 2009, Lim et al., 2012) and longitudinally predict (Walsh et al., 2014) poor cognitive functioning. In contrast, study findings, although small in effect size, implicated blunted rhythms as being associated with improved cognitive functioning, as indexed by the verbal proficiency factor score. Further, verbal proficiency, which in the current study included Vocabulary and Similarities subtest of the WASI, are often considered stable traits that reflect an individual's IQ. Therefore, it is unlikely that lower amplitude directly caused higher verbal proficiency in the current sample. Although the relationship between fragmentation and verbal proficiency did not survive correction for multiple tests, it is likely that similar logic could be applied to that association - increased fragmentation unlikely directly caused an increase in verbal proficiency. Instead, it may be that over time, abnormal RARs encourage individuals to develop improved cognitive strategies or RARs may be influenced by sedentary behavior required by job in the sample. These hypothetical explanations are discussed individually following an interpretation of the impact of gender and race on results.

2.4.1.1 The impact of gender and race

In addition to the unexpected relationship between lower amplitude and higher verbal proficiency, findings were highly influenced by gender and race. Specifically, gender stratified analyses indicated that lower amplitude was associated with both higher verbal proficiency and

verbal learning performance only in women. The addition of verbal learning to significant results was surprising, though may be a result of the common verbal aspect of the two factors. Women have been shown to perform better on verbal tasks (Lewin, Wolgers, Herlitz et al., 2001) and have been shown to have a larger amplitude of circadian modulated cognitive performance compared to men (Shanthi et al., 2015), which together indicate that women may be differentially affected by circadian variation and have higher overall levels of verbal abilities than their male counterparts. Further, race was largely associated with the cognitive factors, which is likely due to the confounding factor of SES and educational opportunity in the current sample (Epps, 1995), and excluding the covariate of race eliminated the statistically significant relationship between amplitude and verbal proficiency. Additionally, there were more non-Caucasian women than non-Caucasian participants men, indicating that race relationships may have had a greater impact on the analyses in women relative to men. Taken together, results may indicate that there may be a complicated interaction between gender and race in their impact on the relationship between RARs and cognition. This is consistent with a previous study that found an interaction between ethnicity and gender impacting sleep duration, indicating that men and women from different ethnic backgrounds may be differentially impacted by the circadian system (Jean-Louis, Kirpke, Ancolie-Israel, Kauber & Sepulveda, 200). Given the small sample size of non-Caucasian men and women, the current sample is not sufficiently powered to explore these potential interactions further. Ultimately, additional research is required to better delineate the potential interaction of gender and race on the relationship between RARs and cognitive factors.

2.4.1.2 Potential reasons for verbal proficiency associations

As reported above, a surprising relationship between blunted amplitude and higher verbal proficiency performance was detected. A small, but internally consistent literature suggests that aberrant circadian functioning may encourage increased general cognitive ability and may aid in understanding results. A meta-analysis of 7 studies, including participants with an average age of 15 to 25 years old, reported a small but significant association (*population correlation* = 0.075, $p < 0.01$) between evening chronotype and higher general IQ (Preckel, Lipnevich, Schneider, & Roberts, 2011). Interestingly, one of the included studies found the association only in women, similar to the current findings (Killgore & Killgore, 2007). Although the exact mechanism behind the association remains unclear, it has been suggested that it may be due to evening chronotype adolescents developing cognitive coping skills to compensate for their circadian misalignment with the imposed school start time (Kanazawa & Perina, 2009). Within the typical school schedule, evening chronotype adolescents are required to function cognitively at a time (i.e., morning) that is not best aligned with their daily peak in cognitive functioning. Due to this cognitive challenge, it may be that individuals with evening chronotype develop important coping skills in order to successfully compensate for being required to function at non-peak time, ultimately leading to improved overall cognitive abilities (Preckel et al., 2011). For example, evening type adolescents and teens may develop alternative mnemonic strategies to remember facts in order to cope with delayed peak cognitive functioning. This is consistent with the literature, which suggests that evening chronotype individuals may be more likely to have more flexible and creative thinking styles than their morning type counterparts (Diaz-Morales, 2007), in addition to higher IQ. Given the association between evening chronotype and abnormal circadian variation (Duffy, Rimmer, & Czeisler, 2001), the evidence may suggest that circadian

disruption, including lower amplitude, may create a necessity in individuals to improve cognitive approaches, resulting ultimately in higher IQ and verbal proficiency scores. However, the overall small effect size of the relationship between evening type and cognitive capabilities and the lack of direct evidence implicating RAR amplitude and increased cognitive coping strategies calls this explanation into question.

A second explanation for the relationship between verbal proficiency and amplitude may be the potential influence of job-related sedentary behavior on RARs. Analyses focused on job type due to the likelihood that verbal proficiency was predictably associated with education (r = 0.23). Further, job type was distributed significantly differently when stratified by gender and race, indicating that factors that had important effects on the amplitude and verbal proficiency relationship also impact job type. Importantly, job type was a significant, but only partial, mediator in the relationship between RAR amplitude and verbal proficiency, while controlling for race and gender, indicating that job type or "prestige" partially explained the relationship between amplitude and verbal proficiency. Although the association between fragmentation and verbal proficiency did not survive correction, job may also explain this relationship as job was a significant mediator in the relationship between RAR fragmentation and the verbal proficiency factor. Although some of the pathway effect sizes were relatively small in both models, the preliminary mediations analyses led us to cautiously suggest that job type may be affecting RARs. Together, analyses of job type support the hypothesis that job may play a role in the relationship between RAR amplitude and fragmentation and verbal proficiency.

We speculate that individuals in "higher" job types may be more sedentary while also more likely to have a higher IQ and verbal proficiency performance. Job type in the current sample was inversely related to amplitude, suggesting that participants in higher "prestige" jobs

had overall lower daily physical activity. Put another way, it may be that job influences the amount of mid-day sedentary behavior an individual exhibits. This may be due to the higher likelihood of sedentary desk jobs in higher job categories. For instance, the highest job type includes engineers, who likely are in more sedentary desk jobs relative to the individuals categorized in the lowest group of unskilled laborers. In addition, given that job also mediated the relationship between fragmentation and verbal proficiency, more sedentary jobs may create larger differences between active and inactive periods (i.e., sitting at a desk vs. commuting) or more "prestigious" jobs may have more unpredictable daily schedules. Importantly, the Hollingshead Classification system used for job categorization used in the current study is imperfect for investigating the association between sedentary jobs and amplitude due to several types of sedentary and non-sedentary jobs categorized together (e.g., one type includes both computer programmers and teachers, and it is presumed that teachers are standing and walking more than those working at a computer). Therefore, these hypotheses could not be directly tested with the present data. Preliminary evidence may suggest that job type may be driving the relationship between amplitude and verbal proficiency.

2.4.2 Lack of RAR association and age interaction with cognition

With the exception of the relationship between RAR amplitude and verbal proficiency, no associations were found between cognitive factors and RARs in the current sample. Further, although age was predicted to moderate RAR impact on cognition, interaction terms were not found significantly. Although, increasing age was associated with lower cognitive scores relative to younger participants in the current sample, which is consistent with previous literature (Salthouse, 2009), the lack of an age moderator effect is likely due to the absence of a main

effect of RARs on cognition. The lack of RAR associations with cognition may be a result of circadian related RAR behavior being obscured in the current sample.

Results from the current study may suggest that the lack of findings may be a result of the "masking" of circadian variation by job-related sedentary behavior. As described in the introduction, masking occurs when a non-circadian, but yet rhythmic behavior is superimposed on, and obscures, behavior that is driven by the circadian clock (Aschoff, 1988). Study 1 *post hoc* analyses led us to speculate that job may be influencing amplitude (and perhaps fragmentation), such that those working in more "prestigious," sedentary jobs may exhibit a blunted daily rhythm of physical activity that would otherwise peak during the typical work day. This may suggest that amplitude and fragmentation of RARS are vulnerable to masking by social constructs in middle-aged samples. Several covariates were included in the study in an effort to correct for masking effects, though did not correct for the current finding. For instance, controlling for average weekly physical activity did not remove this possible confound of sedentary daytime activity and amplitude or fragmentation, likely because an individual can have sedentary daytime activity may have high overall activity levels due to routine exercise. The influence of job on RARs is somewhat consistent with previous findings that employment was significantly related to lower fragmentation, lower stability, and lower amplitude of RARs (Luik et al., 2013; Martin, Jeste, & Ancoli-Israel, 2005). However, both studies failed to collect information on job type and sedentary-related behavior. In general, the potential influence of job on RARs has not yet been explored in the RAR literature, likely due to the majority of RARs being measured in older, retired populations. Given that the study hypotheses were built on the influence of circadian variation on cognition, the potential influence of job may have obscured

our ability to measure circadian functioning in the current sample and may explain the current lack of RAR associations with cognition.

Multiple additional explanations, including limitations in study design and analyses are discussed below (Study 1 Limitations, pg. 59). Further, the lack of findings may be a result of an absence of impact of RARs and/or circadian disruption on cognitive functioning in middle-aged samples. Because these potential explanations apply to both Study 1 and Study 2 results, they are further discussed in the General Discussion (pg. 86).

2.4.3 Subtest associations with RARs

Although composite factor analyses revealed a surprising relationship between lower amplitude and higher verbal proficiency performance, *post hoc* subtest analyses were completed in order to better understand if there may be differential associations with subtests that may have been obscured by the weighting of the individual subtests in the factor analyses. Results revealed that the Stroop Subtest (including Color, Word and Color-Word task) had the most detectable relationships with RARs in the current study, which is consistent with previous findings that suggest that inhibitory control appears to be one of the more strongly circadian-modulated cognitive functions (Burke et al., 2015). However, these results should be incorporated into final results with caution due to their exploratory nature and lack of correction for multiple tests.

First, individuals with an earlier acrophase had better scores (i.e., were able to say more colors in 45 seconds) on the Color task relative to those with a later acrophase. The Color task is thought to be a pure measure of processing speed, as the individual is not required to use psychomotor processing (e.g., Trail Making Task A) or word processing (e.g., Word Stroop Task). In the current study, participants with later acrophase scored worse on this task than their

earlier acrophase counterparts. This is consistent with previous findings in older adult samples, which have found that decreased fragmentation had a medium sized correlation with Color task performance (r = -0.21; Oosterman et al., 2009) while composite scores including the Color task score had small to medium effects (β = 0.35, Oosterman et al., 2009; β = 0.15, Lim et al., 2012). Comparatively, the current study effect size would be considered small (β = -0.11) indicating that acrophase has a lower effect on Color task performance in middle-aged relative to elderly samples. The finding of fragmentation and Color task was not replicated in the current sample, which may be due to the potential impact of job on fragmentation in the middle-aged sample discussed above. Our results suggest that RARs may have a similar or slightly lesser impact on processing speed in middle-aged individuals than the elderly.

In addition, the Color Word Task of Stroop and the Stroop Interference score was also related to RARs. Specifically, greater stability of RARs was associated with more words said in the non-congruent Color Word Task and a better interference score. Both of these indicate that greater stability of RARs was associated with better ability to inhibit automatic responses. This finding is consistent with the association between the nonparametric RAR stability measure and the Color Word Stroop Task in a middle-aged to older adult sample (B = 1.47, Luik et al., 2015), though not consistent with another study that found fragmentation (r = -0.35, medium effect size) but not stability (r = 0.10) significantly correlated with the Color Word Stroop Task (Oosterman et al., 2009). Due to the lack of reported standardized coefficients in the Luik et al., (2015) study, and the mixed findings in the literature, direct comparison with the current study effect (β = 0.11) should be interpreted with caution, though suggest a smaller effect. If replicated, this finding may indicate that performance on the Color Word Stroop Task and interference score may be significantly, but less impacted by RARs, in a middle-aged sample.

There is likely overlap in the potential explanations in the relationship between the Stroop tasks and RARs as there was with the relationship between amplitude and verbal proficiency. For example, it may be that individuals with more "prestigious" jobs have earlier and more stable rhythms due to job schedule predictability and may also be more likely to perform better on tasks that require processing speed and response inhibition.

Although unlikely, we can also speculate that stability and acrophase are less influenced by job-related sedentary behavior than amplitude and fragmentation. For instance, an individual with earlier phase may rise three hours prior to their work start time relative to an evening individual who may wake closer to the same job time. This allows for more variation than the overall limiting nature of sedentary behavior like sitting at a desk that may affect RAR amplitude and fragmentation. If indeed, RAR stability and acrophase are more reflective of the circadian system, RAR stability and acrophase may influence cognition via circadian-related brain mechanisms. For instance, it is likely that unstable and delayed rhythmic firing of the SCN would be indirectly projected to the major arousal system in the brain (locus coerulus; Aston-Jones, Gonzalez & Doran, 2007) and create attenuated vigilance and overall lower cognitive performance. Further, the prefrontal cortex that has often been highlighted as an important brain area supporting Stroop related response inhibition (Vanderhasselt, De Raedt, & Baeken et al., 2009; Vaendrell, et al., 1995), also shows circadian disruption-related morphological changes (Karatsoreos et al., 2011) and may underlie the connection between attenuated response inhibition and RAR stability. In sum, the relationship between stability and acrophase with Stroop task performance could confirm our hypothesis of circadian modulation of cognition, although the potential of several factors including confounding environmental influences on RARs and cognition cannot currently be ruled out.

We are limited in the interpretation of subtests. Associations between RARs and individual subtests are difficult to generalize to broader cognitive domains. For instance, there may be something specific about the Stroop task (e.g., the way that it was administered) that limits generalization to the broader domain of executive functioning. Further, some individual subtests tap into several domains, making it difficult to discuss any one specific domain in results. For example, the Stroop Color Word task requires attention, processing speed, and response inhibition. Lastly, the subtest analyses should be considered preliminary due to the *post hoc* nature of the analyses and the lack of correction of multiple tests. Although findings are consistent with the literature, we do not interpret subtest findings further as a result of the stated limitations.

2.4.4 Associations with WASO

While the lack of statistically significant relationships between RARs and cognitive factors calls into question whether RARs measure circadian functioning in a middle-aged sample, the significant correlations between wake after sleep onset (WASO) and predicted circadian-related cognitive factors (processing speed, working memory, executive functioning, and visual spatial reasoning) may provide an alternative path to investigating circadian contribution to cognition in the current sample. Specifically, a small but significant relationship between higher WASO and lower factor scores (β = -0.08 to -0.10) was found, suggesting that more fragmented sleep was associated with poorer performance on cognitive factors relative to more continuous sleep. Multiple factors contribute to WASO, including the circadian system and sleep homeostasis, though they both must be properly aligned for optimal sleep (Dijk & Czeisler, 1995). Circadian disruption affects this alignment and poor alignment creates difficulties in maintaining sleep,

thereby indicating that increasing WASO may be a result, at least in part, to circadian disruption. Further, WASO has been associated with several markers of circadian desynchrony, including larger time between melatonin onset and midsleep (Yongstedt, Kripke, Elliot, & Kaluber, 2001), larger differences between amplitude and the mesor of RARs (Lee, Lee, Aycock & Decker, 2010), and poorer circadian rhythm strength as measured by 24-hour autocorrelation of RARs (Lee et al., 2015). Additionally, WASO was associated with clock gene polymorphisms that were associated with circadian rhythm strength (Lee et al., 2015), suggesting the same clock genes that disrupt circadian rhythmicity also may increase the amount of WASO experienced. Although several factors likely impact amount of WASO, including depression, physical activity, and depression, WASO was likely not as easily masked by sedentary job as RARs in the current sample. This may mean that significant correlations with cognitive factors may indicate that WASO reflects an important interaction between sleep and circadian influences on cognition in middle-aged adults.

Interestingly, this finding extends the current literature investigating the impact of actigraphy measured WASO on cognition, which has been mostly limited to older and young adult samples. For instance, increased WASO has been found to be significantly associated with poorer executive task performance (Stroop Interference and Trail Making Task B) above and beyond total sleep in healthy older adults (Blackwell et al., 2006; Blackwell et al., 2013; Naismith et al., 20019; Cochrane, Robertson, & Coogan, 2012). This is consistent with our findings, as we control for total sleep duration as well. In older adult samples with insomnia, higher WASO has been associated with lower performance on recall tasks (Wilckens et al., 2016) and improvement in WASO following insomnia treatment has been associated with improvement on a task switching paradigm (Wilckens et al., 2017), suggesting a potential causal

link between increased night awakenings and poorer cognitive performance. In addition, studies investigating differences between young (21-30 years old) and older adult (55-77 years old) samples in the relationship of WASO and cognition, has found higher WASO to be associated with task switching performance in both age groups (Wilckens et al., 2014a), associated with executive tasks only in younger samples (Wilckens et al., 2014b), and associated with verbal learning only in the older the older sample (Wilckens et al., 2014b). WASO likely impacts sleep via its negative impact on sleep efficiency and progression through sleep stages, which also has been shown to impact cognition. Of note, few studies have investigated impacts of WASO on cognition in healthy middle-aged adults, with one study finding increased sleep awakenings associated with cognitive impairment in middle-aged males (Waller & Jennum, 2013). The lack of research in linking cognition and actigraphy measured WASO in middle-aged adults may indicate the unique and a potential valuable contribution of results to the literature. The associations of WASO, while controlling for total sleep duration, with processing speed, executive functioning, visuospatial reasoning, and working memory extend the current literature to healthy middle-aged adults and offer an interesting line of future research (further explored in the Study 1 Future Directions, pg. 62).

2.4.5 Summary

Primary study hypotheses were not supported, given the lack of association between RAR variables and main cognitive factors of interest (processing speed, executive functioning, visuospatial reasoning, and working memory) in study models. Instead, an association was detected between amplitude and verbal proficiency in the opposite direction predicted. *Post hoc* mediation analyses suggested the sedentary job-related behavior may partially explain the

relationship between amplitude and verbal proficiency, supporting a hypothetical masking effect of job or sedentary behavior on RARs. In addition, *post hoc* subtest analyses indicated a preliminary relationship between RAR acrophase and stability with the Stroop subtasks (Color, Color-Word, Interference score) that replicates findings in the literature. Further, preliminary findings suggest that higher WASO, which may reflect poor alignment of circadian and sleep drive, is associated with attenuated executive functioning, visuospatial reasoning, and working memory in middle-aged adults.

2.4.6 Study strengths and limitations

Importantly, the AHAB II sample was chosen due to its many strengths. First, the AHAB II sample is rare in that it collected both actigraphy and cognitive variables in a large number of individuals. Second, the neuropsychological assessment battery was extensive in this sample, and testing time was recorded, allowing for the investigation of several cognitive domains while controlling for time of testing given strong evidence of daily variation in cognitive functioning reviewed above. Third, the sample is extremely well phenotyped group of middle-aged healthy adults, allowing for the associations between RARs and cognition to be explored in a previously untested age group, and the ability to control for several important confounding factors in the relationship.

Additional study limitations may explain why study hypotheses were not supported and limit the interpretation of results. First, the cross-sectional design of the study eliminates our ability to determine if circadian desynchrony anticipates cognitive decline. Further, the observational design without experimental manipulation means that the results were vulnerable to confounding variables. A prominent example of this is the hypothesized masking by sedentary

behavior on the expression of daily activity and consolidation of such activity. Additional confounding factors may include differing levels of stress or the amount and timing of social interactions, which both may influence individual circadian disruption as well as cognition.

Next, because the study was not originally created to test associations between actigraphy and neuropsychological performance, the duration of time between actigraphy collection and neuropsychological assessment differed by individual. The varying amount of time between neuropsychological assessment and actigraphy collection may have weakened our ability to detect effects. However, several points lead us to believe that neuropsychological scores should have remained fairly stable in the current sample. Performance on neuropsychological assessment is thought to be fairly stable and only changes greatly due to major shifts in health status (Calamia, Markon, & Tranel, 2013), suggesting that overall large variations in cognitive performance should not occur in the current healthy sample across a time frame of 0-139 days (M = 54.34 days, SD = 22.61), which occurred between neuropsychological testing and actigraphy . Further, seasonal changes, which have been found previously (Meyer et al., 2015), were not observed in the current sample, as day length was not significantly associated with any of the cognitive factors. Therefore, changes in day length between actigraphy and assessment are unlikely to have impacted cognitive performance. Together, evidence suggests that the duration between actigraphy and neuropsychological testing did not impact our ability to detect relationships between RARs and cognition, though the impact of this limitation cannot be completely ruled out.

In addition, the current study standardized the neuropsychological scores to the sample norms instead of standardizing scores by age and other demographics at a population level. This was necessary due to the aim of exploring interactions between RAR measures and age. Because

individuals who are older will tend to perform more poorly on the assessments, it may be that controlling for age and education greatly decreased variation to be explained by changes in circadian timing across the lifespan (Salthouse, 2009; Salthouse, 2011), and subsequently our variables of interest. Future research could easily investigate whether norming by age group and years of education, thereby negating the need to control for age and education as covariates, would lead to different results. Further, the AHAB II sample is a healthy sample and therefore the current study could only investigate variation in normative cognitive performance and was unable to explore possible associations with cognitive deficits that would be likely if the sample hadn't excluded such illnesses (e.g., major neurological disorder, cardiovascular disease, schizophrenia and bipolar disorder).

The current study also did not separate workday and non-workdays in actigraphy data. This was due to the decision to include both non-workday and workday data in the nonparametric rhythm measures in order to capture the full range of variation in RARs across available workday and non-workday data (Blume et al., 2016). It is possible that the extended cosine measures, especially acrophase, may change day-to-day, and averaging across days may attenuate the ability to find effects with this variable that we would have seen if we had calculated and tested acrophase for work-days and non-work-days separately. However, a *post hoc* analysis using a measure of the difference between acrophase on workdays vs. non-workdays (i.e., social jet lag; SJL) found no significant association between SJL and any of the cognitive factors predicted to be associated with RARs, suggesting that the difference between work day and non-workday rhythms would not have affected the relationship between RARs and cognitive factors. Regardless, separating the data for work-days and non-work days may yield different results, though the SJL analysis suggests the analyses would not be fruitful. In the case

of masking by sedentary midday behavior, using non-work day data, if enough such days were available, might allow us to determine if amplitude were higher, and fragmentation reduced on non-work days.

Lastly, *a priori* analyses based on RAR associations with cognition in older adult samples indicated that the sample was sufficiently powered. However, the effect sizes (β = 0.03 to 0.08 for extended cosine analyses and β = 0.01 to 0.03 for nonparametric analyses) observed in the current sample were smaller than those reported in the previous studies investigating associations between RARs and cognition in older individuals (β = 0.22 to 0.27 for extended cosine analyses and β =0.08 to 0.35 for nonparametric analyses), perhaps as a result of changes in circadian rhythmicity of clock genes in brain tissue due to older age in the elderly samples (Chen et al., 2015) and a potential higher impact of RARs on cognition in older age (Luik et al., 2015). Using the smaller, observed effect sizes in *post hoc* power analyses revealed that both extended cosine and nonparametric analyses were underpowered to detect associations between RARs and cognition.

2.4.7 Future directions

Future research should focus on developing a better understanding of the impact of daily sedentary behavior due to desk jobs or other environmental influences on RARs that may be specific to middle-aged samples. One study investigating how participant factors impact nonparametric measures of RARS in a sample with both middle-aged and older individuals found that stability and fragmentation was associated with employment (Luik et al., 2013), though the few studies that have investigated RARs in middle-aged have not analyzed job type as a study covariate (e.g., Berger et al., 2010; Berle, et al., 2010; Dhruva et la., 2012; Huang et

al., 2002; Levin et al., 2005; Savard et al., 2009). Future RAR research should include a detailed participant self-report of job type and job schedule to determine if an individual is restricted from engaging in physical activity in order to perform job duties. A questionnaire or interview that aimed to quantify the amount of sedentary versus active periods due to job and the predictability of an individual's job schedule would be important to better understand if and how job is impacting RARS. Then, if our hypothesis is confirmed, and RARs are impacted by job, these data should be used as covariates in future RAR research aiming to identify circadian functioning. Detailed job information will help clarify if job has a masking effect on RARs in middle-aged samples and further clarify if RARs are associated with cognition in future studies.

Alternatively, it could be possible to collect actigraphy on multiple sequential weekends or periods of non-work days, in an effort to avoid potential masking of RARs by job-related sedentary behavior. If masking by employment variables cannot be avoided, it may be that RARs collected from actigraphy is not a feasible way to estimate circadian rhythms in samples that are typically employed or in school (i.e., working age or school age), and should be restricted to samples that are free to engage in activity and not restricted by employment (i.e., those unemployed due to disability or retirement).

However, the current study points to the potential value of WASO as combined measure of sleep and circadian functioning. WASO, like RARs, can be easily, non-invasively, and inexpensively measured through wrist actigraphy in large samples. Future research exploring whether WASO mediates an association between circadian variation and cognition may help to elucidate this hypothesized impact of circadian variation on cognition in middle-aged samples. Specifically, it would be interesting to test whether higher variability in circadian timing (i.e., standard deviation of rhythm, acrophase, or midsleep times) was associated with cognitive

functioning and whether WASO mediated the relationship. Given that WASO increases with age, and women tend to experience more WASO than men (Ohayon, Carskadon, Guilleminault & Vitello, 2004), gender and age would necessarily be included as covariates. Given that variables other than circadian disruption may impact WASO and cognition, including depression and physical activity, these will also be important covariates to include in any follow-up analyses. We further propose that studying both sleep and circadian timing in concert would be ideal, as was attempted here, as sleep research that doesn't take circadian timing into account, and circadian research that ignores sleep duration are both missing potential explanatory variance that interact to influence behavior, mood, and health (e.g., Wright et al., 2012; Buxton et al., 2012; Boivin et al., 1997).

2.4.8 Conclusions

Study hypotheses predicted that delayed, blunted, fragmented, and unstable RARs would be associated with poorer cognition in a middle-aged sample, due to the relationship between circadian dysfunction and poor cognition in animal studies and small laboratory settings. RARs were thought to be a noninvasive way to measure circadian functioning in a large sample. In contrast, results did not support a relationship between RARs and cognitive factors in the current sample, and may indicate that RARs in middle-aged samples are vulnerable to masking by job-related sedentary behavior. Preliminary evidence may suggest WASO may be an advantageous alternative path to better understanding the intersection of sleep homeostasis and circadian functioning on cognition in middle aged adults, highlighting and interesting area for further research.

Given the prevalence of employment in middle-aged individuals and the current lack of controlling for sedentary job-related behavior in RAR analyses in middle-aged samples, the finding points to an additional important avenue for future research. Further understanding of the impact of sedentary behavior on RARs will enable us to better understand if this masking can be controlled for in some way, or if it obviates the use RARs as proxy for circadian functioning in a working, middle-aged sample. The vulnerability of RARs to masking effects of job in a middle-aged sample remains an under-researched, yet important area, and needs to be managed prior to making conclusions about RARs as proxies for circadian functioning.

3.0 STUDY 2

3.1 AIMS AND HYPOTHESES

Study 1 aimed to better understand the relationship between RARs and cognition in a middle-aged sample in order to elucidate the potential impact of circadian dysfunction on cognition in this age-range. Study two was included in order to extend the current literature to a younger sample. Previous studies investigating the association between circadian variation and cognition in young adults has been limited to small, laboratory settings, restricting the generalizability of the results. A better understanding of the relationship between RARs and cognition in younger samples would not only elucidate potential targets for improvement of everyday cognitive functioning in healthy groups but also provide potential targets of further research and intervention for populations with pathological cognitive functioning.

Given that younger adults' cognition may be more affected by circadian disruption than older adults, especially in the domains of processing speed and visuospatial ability (Bonnet, 1989; Rowe, Hasher, & Turcotte, 2009; Silvia et al., 2010), these cognitive domains were specifically targeted as primary domains of interest. In addition, reaction time, which has not yet been associated with RARs, though has been shown to have a strong circadian component and impacted by misalignment (Van Dongen & Dinges, 2000; Wright et al., 2002; Zhou et al., 2011; Burke et al., 2015) was included as primary domain of interest. In contrast, and similar to Study

1, we included verbal memory as a secondary domain and predicted the composite score would not be associated with RARs. The specific aims for the project were as follows:

1. To test whether rhythm measures of RARs including amplitude, acrophase, and robustness of rhythm are associated with the primary cognitive domains and not the secondary domain. It was predicted that individuals with lower amplitude, later acrophase, and less robust rhythms would have lower scores on processing speed, reaction time, and visuospatial tests relative to those with higher amplitudes, earlier acrophase, and more robust rhythms. It was also predicted that amplitude, acrophase, and robustness of rhythms would not be associated with verbal memory.
2. To test whether non-parametric measures of RARs including both day-to-day variation and the amount of fragmentation of RARs are associated with primary cognitive domains and not the secondary domain. It was predicted that those with higher variability between days and greater fragmentation would be associated with lower measures of processing speed, reaction time, and visuospatial abilities relative to those with more stable and less fragmented rhythms. It was also predicted that neither day-to-day of variation nor fragmentation would be associated with verbal memory.

3.2 METHODS

3.2.1 Participants and design

The Effects of Dose-Dependent Sleep Disruption on Fear and Reward Study (SFeRe) was used to investigate the second project aim. For SFeRe, participants aged 18-30 years old were recruited for a longitudinal sleep deprivation and imaging study. Participants were excluded if (a) they had a history of or current mood and/or sleep disorder, alcohol/substance abuse or dependence, psychotic disorder, sleep apnea, seizure, or neurological disorder, (b) current use of prescribed or over-the-counter medication known to affect sleep, (c) had sleep apnea as measured by an in home study using a portable two channel apnea screening device (Apnea Link Plus; ResMEd Corporation Poway, CA) (d) current diagnosis of diabetes or high fasting glucose levels, (e) current night shift work, (f) average caffeine intake >2 beverages per day, (g) color blindness or hearing impairment, or (h) standard exclusion criteria for imaging such as metal implants. Important for the current study, individuals were excluded if they exhibited irregular sleep-wake cycles during actigraphy measurement period (i.e., more than 30 minutes variance in sleep and wake up times and/or < 6 hour or > 9 hours of sleep), or if they reported extreme evening chronotypes (22 > Composite Scale of Morningness). Informed consent was obtained in accordance with the guidelines of the University of Pittsburgh Institutional Review Board. Participants were given actigraphy devices (Actiwatch -2, Philips Respironics; USA) to wear for a seven-to ten-day monitoring period prior to a baseline neuropsychological assessment.

3.2.2 Neuropsychological assessment

The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT: Maroon et al., 2000) provides a brief, 20 minute computerized measure of individual neuropsychological functioning and was administered at baseline. The ImPACT includes five separate subtests that are used to calculate five composite scores (Henry & Sandel, 2014). One composite score, impulse control, which is used as a measure of test validity (Iverson, Lovell & Collins, 2005; Gerrard et al., 2017), had extremely restricted variance due to above average performance, and was not used as a composite score in primary study analyses. Composite scores were created based on the following ImPACT subtests according to previously established methods (see Table 23; Henry & Sandel, 2014; Stocker, Kahn, Henry & Germain, 2017).

Table 23. Composite and subtest score averages

Composite Score	Mean Score	Standard Deviation
Verbal Memory Composite	91.51	6.62
Word Memory % Correct	95.5	4.16
3 Letters % Correct	94.72	4.33
Symbol Match Correct (Hidden)	7.59	1.38
Visual Memory Composite	67.23	10.43
Design Memory % Correct	80.5	10
XO Memory % Correct	71.97	21.2
Reaction Time Composite	0.59	0.09
XO Average Correct RT	0.59	0.06
Symbol Match Average Correct RT	1.43	0.6
Color Match Average RT	0.69	0.09
Visual Motor Speed Composite	40.50	5.86
XO Correct Taps (Interference Task)	11.97	0.16
3 Letters # Correct (Interference Task)	20.69	3.89

3.2.2.1 Primary domains

Visual Memory. Visual memory was calculated from two subtests, including design memory and location match of X's and O's. In design memory, a series of line designs are presented to the participant. The design memory percent correct subtest score represents percentage of correct identification of previously displayed designs in both the immediate and delay conditions. In the X's and O's task, participants are required to remember placement of three X's in a screen of X's and O's after a distractor task. The XO memory percent correct response represents the percentage of correctly identified XOs after distractor task. The design memory percent correct and XO memory percent correct was averaged for a percent score representing design memory. The composite score was calculated by adding the design memory percent correct and XO memory percent correct together and dividing by two. Higher percentage scores on the visual memory composite score reflect better performance. The visual memory composite score has been shown to be moderately correlated with performance on the both the total and delay trials of the Brief Visuospatial Memory Test (BVMT; r = 0.38 & r = 0.35 respectively; Allen & Gfeller, 2011).

Reaction Time. Reaction time was calculated from the average reaction time of the symbol match task (Symbol match average correct reaction time), which requires participants to use a number-symbol key to select a number corresponding with the presented symbol. The composite score also includes reaction time from the color match task that is similar to the Stroop task. Participants indicated when word and color were congruent and provided no response when color and word were incongruent. Average color match reaction time was calculated as the average across all trails. Lastly, an average of reaction time for the correct

identification of symbols during the distractor task of X's and O's task was included in the reaction time composite score (XO average correct reaction time). Reaction time composite score was then calculated as the addition of the symbol match reaction time, average color match reaction time, and XO average correct reaction time divided by three. The reaction time composite score has been found to be highly correlated with the symbol digit modalities test (r = -0.60; Iverson et al., 2005), a task that is often associated with processing speed and psychomotor abilities. Lower reaction time composite scores represented better performance.

Visual Motor Speed. The visual motor speed composite score, sometimes referred to as the processing speed composite score in the literature (e.g., Iverson et al., 2005), was calculated from the correct number of taps during the X's and O's interference task (XO correct taps). Specifically, participants were required were presented with multiple shapes and only were to tap the screen when a target shape was presented. This score was divided by four. In addition, the distractor task for a task that required participants to remember three letters, which required delayed recall of three letters following a distractor task of counting backwards from 25 was included. The amount of numbers correctly counted during this task was also included in the subtest (3 Letters # Correct). This score was multiplied by three in order to represent scores from all three trials and added to the XO correct taps score. The total was divided by 2 for an average number of correct taps for each distractor task. Higher scores reflected better performance on this composite score. This composite score has been found to be highly correlated with performance on the symbol digit modalities test (r = 0.70; Iverson et al, 2005) and Trails B (r = -0.38; Allen & Gfeller, 2011).

3.2.2.2 Secondary domain

Verbal Memory. Verbal memory was calculated using the word memory subtest, which consisted of 12 words flashed on a screen following a forced recall section during which the participant was asked if a certain word was part of the original list. There was also a delayed recognition recall that allows for the measure of both immediate and delayed recall. The percent correct of both the immediate and delayed recall was included in the verbal memory composite (word memory percent correct). The three letters percent correct subtest was calculated as the percent of numbers recalled correctly across trials. Lastly, the number of correct symbol matches made during the symbol match task was included (symbol match percent correct). Percent scores were summed and divided by three for an average percent score. Higher percent scores on the verbal memory composite score represent better functioning. The verbal memory composite score has been found to be moderately correlated with performance on the Hopkins verbal learning test-revised (total words remembered, $r = 0.27$; following delay $r = 0.31$; Allen & Gfeller, 2011), which is similar to the Rey Verbal Learning Test used in Study 1.

3.2.3 Actigraphy collection, preprocessing and analysis

Participants were asked to wear an actiwatch for at least 7 days and instructed to not remove the watch. Actigraph cleaning and data preprocessing protocols were consistent with Study 1 (see above, pg. 27). Actigraph data was used to both calculate RAR measures and extract covariates (total sleep time and wake after sleep onset) using integral actigraphy algorithms. For both extended cosinor analyses and nonparametric analyses, RAR modeling was completed in the same manner as described above for Study 1 (pg. 27- 30). Amplitude, acrophase, and the pseudo

F statistic was extracted and used as dependent variables for Aim 1. IV and IS were used as dependent variables in Aim 2.

3.2.4 Covariates

Age, sex, and the ranking for six categories of years of education (i.e., (1) 5th grade or less, (2) 6th-11th grade, (3) 12th grade or GED, (4) some college, (5) a completed college degree, or (6) graduate/professional degree) were used as demographic covariates. Race was collected via self-report and categorized as Caucasian (reference group) vs. Non-Caucasian. In addition, the following covariates were selected *a priori* due to their association with RARs, cognition, and their standard use in the literature. Given that these covariates mirror those used in Study 1, the justification for including each covariate is the same as the justification of using the covariate in Study 2 (see pg. 30). Time of testing, the sleep variables, and body mass index were measured in the same way as Study 1. The remaining covariates represented the same factor but were collected in slightly different ways, as listed below.

Employment status. Individuals were assigned an employment status as unemployed, student, part time employed, or full time employed. The reference group was the unemployed/student group.

Physical activity. In order to control for potential effects of exercise, participant self-reported minutes of exercise was extracted from sleep diary logs. Times were averaged over number of days of actigraphy to extract average weekly exercise. If a participant did not provide any number for this section, they were assumed to have no exercise for a given day.

Depression. The Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, Williams, 2001) was used to measure overall depression symptom number and severity. Scores on the

PHQ-9 range from 0 to 27. Similar to the CES-D in Study 1, the sleep question was removed form the total and then summed in analayses in order to avoid the confound of the sleep variables already included. The total score was propsoed to be used as a conintuous covariate. As will be discussed below, scores were extremely limited on the PHQ-9 in this sample and the covariate was ultimately dropped from the model.

Alcohol consumption. Participants reported number of drinks consumed on each day of actigraphy collection via sleep diaries. This number was summed and divided by the number of days of actigraphy to provide a daily average consumption of drinks of alcohol per participant. Similarly, alcohol use was low in the sample and, as described below, was not included as a covariate.

Smoking status. Participants also reported number of cigarettes smoked per day via sleep diaries. If an individual reported smoking at all during the actigraphy period they were categorized as a current smoker. All others were labeled as non-current smokers. Non-smokers were the reference group. Again, the number of smokers in the current sample were low and the variable was ultimately dropped from the models.

In total 153 individuals enrolled in the study. Out of these, 35 did not complete ImPACT, eight did not have at least four full usable days for actigraphy (due to watch malfunction), and one participant did not have complete covariate data. A total of 109 participants were included in study analyses.

3.2.5 Statistical approach

Consistent with the Study 1 approach, all variables of interest were winsorized to the third standard deviation. Correlations were run between RAR measures, ImPACT composite scores

and covariates. Due to skew in the ImPACT scores, as a result of participants obtaining close to maximum scores on the majority of subtests, nonparametric spearman's correlations were used to reduce the impact of non-normally distributed data.

To investigate Aim 1, a form of robust regression utilizing 95% bias corrected and accelerated confidence intervals was used due to non-normally distributed residuals of OLS regression models (Carpenter & Bithell, 2000; Fields, 2012;). This was due to the amount of skew exhibited by the composite scores (Figure 9), which was unable to be corrected via transformations. A hierarchical regression model was built predicting each composite score in the same way as in Study 1. However, for varied reasons described in the first paragraph of the results section, covariates included were slightly changed. Step one included the demographic factors of age, sex, years of education, and employment status. Step two included weekly activity, WASO, and TST. Step three included BMI. Finally, step four included acrophase and amplitude. Similar to Study 1, analyses including the pseudo *F* statistic in the fourth step were run separately due to high correlation with amplitude (r_s = 0.63, $p < 0.001$) and included in Appendix B. No significant differences from those reported here were found. To investigate Aim 2, the same hierarchical regression models were created with the exception that in step four the nonparametric measures, IV and IS, were included. Similar to Study 1, these represent a slight deviation of the covariates originally proposed. Appendix A summarizes findings from originally proposed models, which exhibited the same pattern of finding as those reported here. Consistent with Study 1, Benjaminin & Hochberg correction was used (p = 0.04). All statistical analyses were completed in SPSS version 24 (IBM, 2016).

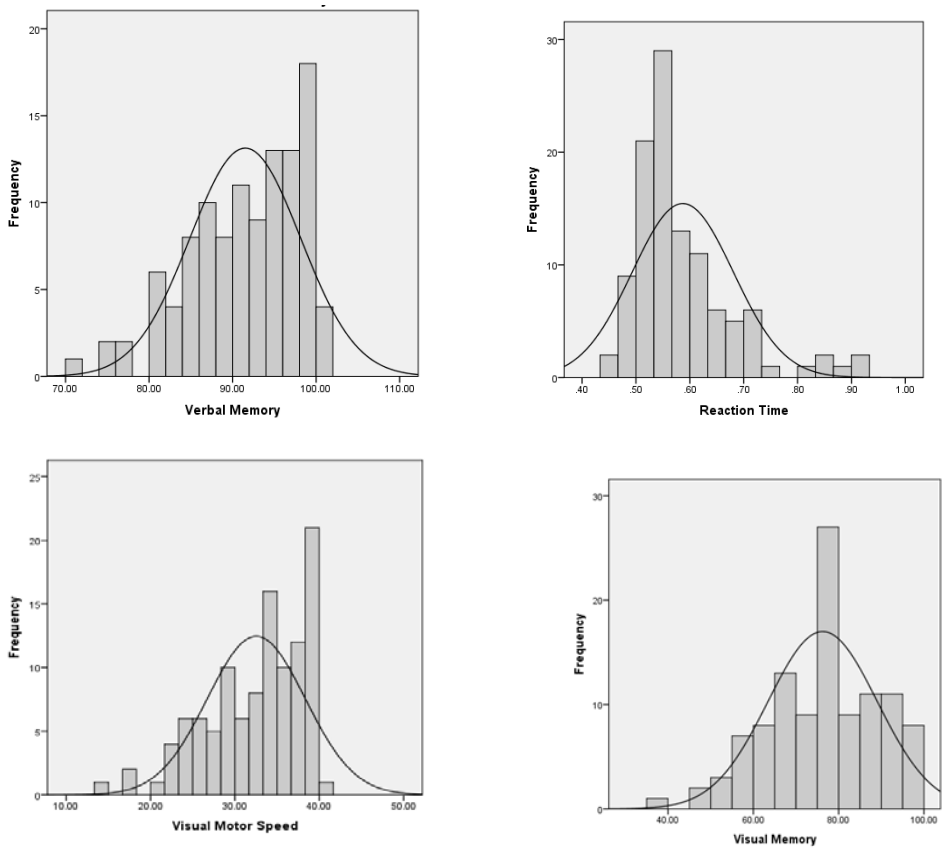

Figure 9. Histograms of ImPACT composite scores. Normal distribution curve included for reference. Histograms, especially for Verbal Memory (A) and Visual Motor Speed (C) composite scores, show ceiling effect in performance. Reaction time scores are skewed closer to faster times.

3.3 RESULTS

Table 24 summarizes demographics for the 109 participants included in the SFeRe sample. Overall, the average age of the sample was *M* = 23.74 years (*SD* = 3.32), and participants either completed some college or completed a college degree. Almost half (45.9%) of the sample was unemployed or a student. The average PHQ-9 score was below one point and the maximum was four, which is below the minimal cut off score of five for minimal depressive symptoms

(Kroenke, Spitzer, Williams, 2001). Further, fewer than 10% of the sample were current smokers (6%) and 90% of the sample had on average less than one alcoholic drink a day. Actigraphy ranged from four to fourteen days, with an average of eight days collected. Spearman's correlations are included in Table 25, although none of the covariates were consistently associated with the ImPACT subscales.

Table 24. SFeRe study demographics (*n* = 109)

Variable	Mean	SD
Age	23.74	3.32
Female, n (%)	62 (56.9%)	
Years of School, n (%)		
12th or GED	3 (2.8%)	
Some College	40 (36.7%)	
College Degree	49 (45.0%)	
Graduate/Professional Degree	17 (15.6%)	
Job Status		
Student/Unemployed	50 (45.9%)	
Part Time	42 (38.5%)	
Full Time	17 (15.6%)	
Caucasian, n (%)	71 (65.1%)	
Exercise	54.84	75.71
BMI	23.92	3.71
PHQ9	0.5	0.92
Daily Avg Alcohol	0.31	0.43
Current Smoker, n%	6 (5.5%)	
TST	411.34	39.38
WASO	40.19	12.94
Amplitude	89.94	44.52
Acrophase	15:31	0:37
F	3698.04	1922.98
IV	0.84	0.22
IS	0.51	0.11

Note. BMI= Body mass index, TST = Total sleep time, WASO= Wake after sleep onset, IS= Interdaily stability, IV= Intradaily variability, PHQ9 = Patient Health Questionnaire -9. Exercise is in average daily minutes.

Table 25. Spearman's correlations between study covariates, RAR measures, and ImPACT composite scores

Variable	IS	IV	Acrophase	Amplitude	F	Verbal Memory	Visual Memory	Reaction Time	Visual Motor Speed
Age	-0.01	-0.09	-0.18	0.00	-0.01	-0.12	-0.01	-0.13	0.12
Gender	0.22*	0.01	-0.11	0.07	0.11	-0.01	-0.05	0.10	0.14
Race	-0.40**	0.33**	0.13	-0.36**	-0.27**	0.04	-0.12	0.26**	-0.17
Education	-0.05	0.03	-0.13	-0.02	0.05	-0.16	-0.02	-0.21*	0.16
Job Status	0.12	-0.27**	-0.33**	0.23*	0.02	-0.01	0.00	0.00	-0.13
Exercise	-0.23*	0.11	0.09	-0.08	-0.14	0.06	0.12	-0.07	0.29**
WASO	0.15	-0.05	-0.01	-0.12	-0.05	-0.12	0.21*	-0.17	0.03
TST	0.07	-0.10	-0.06	-0.05	-0.03	-0.02	-0.04	-0.03	0.12
BMI	0.08	-0.10	-0.14	0.02	-0.04	0.05	0.06	-0.15	0.02
PHQ9	-0.05	0.20**	-0.13	-0.09	-0.021	0.03	-0.04	0.07	0.03
Alcohol	-0.05	-0.01	-0.03	0.15	0.05	0.02	0.11	-0.16	0.11
Smoking Status	0.07	-0.15	-0.02	0.03	-0.07	0.16	-0.05	0.10	-0.06

It is important to note that some of the *a priori* selected covariates in the sample were removed from the models. Specifically, due to the low, nonclinical levels of depression, PHQ-9 was not included in the models. Further, as a result of overall low drinking rates and few people reporting smoking in the week of actigraphy, smoking and drinking measures were also excluded from analyses. Importantly, both average daily alcohol and smoking status were not significantly correlated with either RAR measures or ImPACT composite scores.

In addition, due to a technical problem with the ImPACT time stamp, there was only an accurate time stamp at the start of ImPACT for 69 (63.3%) participants. As a result of a large number of individuals that would need to be excluded from the model if testing time was included, the covariate was removed from the model. Importantly, all recorded ImPACT testing times occurred between 4:15PM and 9:00PM and testing time was not significantly correlated with any of the cognitive composite scores (Table 26). Results from primary analyses only in the individuals who had the correct testing time did not differ from those described below.

Table 26. Available testing time correlations with ImPACT composites scores

	Verbal Memory	Visual Memory	Reaction Time	Visual Motor Speed
Testing Time	-0.06	-0.09	0.06	0.01

3.3.1 Aim 1: Extended Cosine Analyses

The extended cosine analyses could not converge for one participant in the sample, so the analyses were run on the remaining 108 participants. Figures 10 and 11 depict extreme amplitudes and acrophases in the sample. When investigating correlations between amplitude and acrophase with study covariates (Table 25), being employed was significantly associated with earlier acrophase (r_s = -0.33, p = 0.001). Additionally, employment (r_s = 0.23, p = 0.001) and being non-Caucasian (r_s = -0.36, p < 0.001) were associated with lower amplitude. Neither amplitude nor acrophase were associated with any of the ImPACT composite scores (Table 27).

Table 27. Spearman's correlations between RAR measures and ImPACT composite scores

	Verbal Memory	Visual Memory	Reaction Time	Visual Motor Speed
IS	-0.10	0.09	-0.13	0.00
IV	-0.02	0.02	-0.09	0.05
Acrophase	-0.04	-0.01	0.04	0.01
Amplitude	-0.10	0.02	0.02	-0.09
F	-0.12	0.03	-0.02	-0.14

Note. IS= Interdaily stability, IV= Intradaily variability

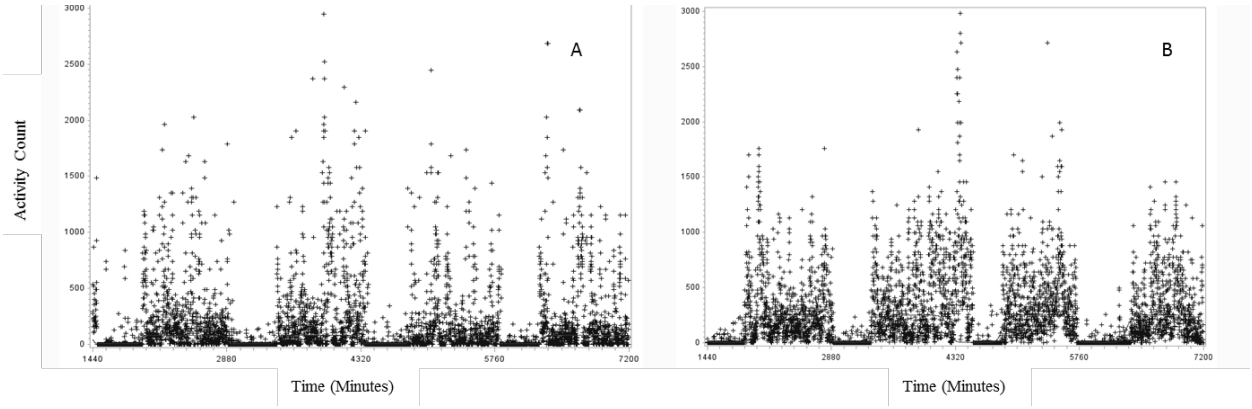

Figure 10. Examples of high and low amplitudes in the Study 2. A. Depicts a participant who had a lower amplitude in the sample (54) B. Depicts a participant with one of the higher amplitudes in the sample (218).

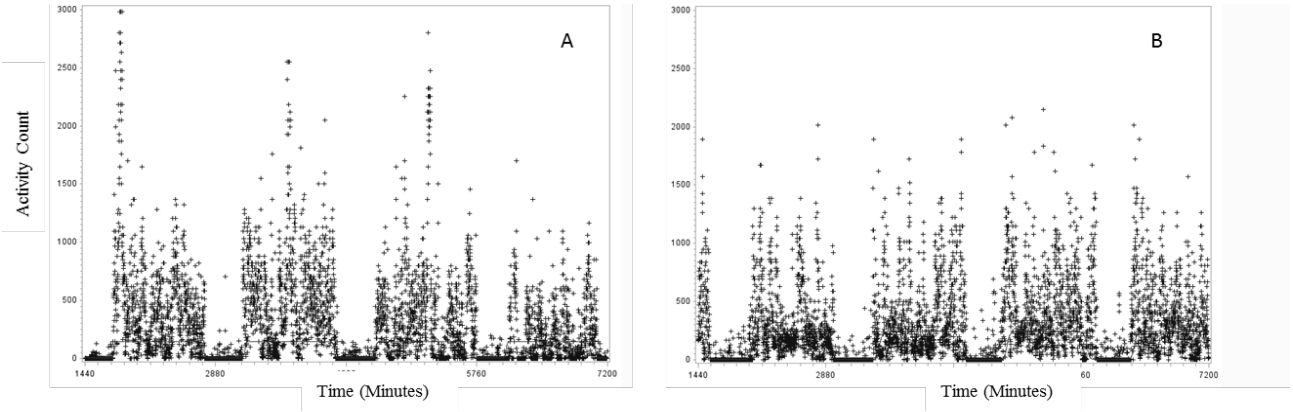

Figure 11. Examples of early and late acrophase in Study 2. A. Participant who exhibited an early acrophase (13:43). B Participant who exhibited a late acrophase (17:40).

3.3.1.1 Hierarchical regression models

Verbal memory. All of the steps of the models predicting verbal memory were not significant and therefore coefficients were not interpreted.

Visual memory. All of the steps of the models predicting visual memory were not significant and therefore coefficients were not interpreted.

Visual motor speed. The second ($F_{(8,107)} = 2.35$, $R^2 = 0.16$, $p = 0.02$) third ($F_{(9,107)} = 2.07$, $R^2 = 0.16$, $p = 0.04$), and fourth step ($F_{(11,107)} = 1.99$, $R^2 = 0.19$, $p = 0.04$; Table 28) of the models were significant, though ΔR^2 was not significant at any step. Amplitude and acrophase were not significant in the fourth step of the model.

Table 28. Step 4 of robust regression predicting the visual motor speed composite score

Variable	b (CI)	SE B	β
Age	0.20 (0.25- -0.26)	0.25	0.11
Gender	2.34 (-0.46-5.07)	1.29	0.20
Race	-2.22 (-4.67-0.45)	1.32	-0.18
Education	0.63 (-1.53-2.86)	1.08	0.08
Job Status	-0.92 (-2.32- 0.48)	0.71	-0.11
Exercise	0.02* (0.00-0.04)	0.01	0.23
WASO	0.02 (-0.07-0.10)	0.05	0.05
TST	0.02 (-0.01 - 0.05)	0.02	0.12
BMI	0.04 (-0.21 -0.28)	0.14	0.02
Amplitude	-0.02 (-0.05- 0.01)	0.02	-0.15
Acrophase	0.92 (-1.36 - 2.92)	1.06	0.10

Note. * $p < 0.05$, b= bootstrap coefficient, SE = Standard Error, CI= Bias corrected confidence intervals, β = standardized coefficient, WASO = Wake after sleep onset, TST = Total sleep time, BMI= Body mass index. Includes 95% Bias corrected and accelerated confidence intervals in parentheses. Confidence intervals and standard errors based on 1000 bootstrap samples

Reaction time. The first ($F_{(5,107)} = 2.52$, $R^2 = 0.11$ p = 0.03), second ($F_{(8,107)} = 2.11$, $R^2 = 0.20$, $p = 0.04$), third ($F_{(9,107)} = 2.66$, $R^2 = 0.20$, $p = 0.01$) and fourth step ($F_{(11,107)} = 1.99$, $R^2 = 0.20$, $p = 0.02$, Table 29) was significant in the model. Again, ΔR^2 was not significant at any step. Amplitude and acrophase coefficients were not significant. As shown in Table 29, the significant variables driving significant model steps were education and BMI.

Table 29. Step 4 of robust regression predicting the reaction time composite score

Variable	b (CI)	SE B	β
Age	0.01 (0.00 -0.02)	0.00	0.21
Gender	0.01 (-0.03 - 0.05)	0.02	0.06
Race	0.04 (0.00 - 0.08)	0.02	0.18
Education	-0.04* (-0.08 --0.01)	0.02	-0.33
Job Status	<0.01 (-0.03 - 0.02)	0.01	-0.01
Exercise	<0.01 (-0.01- 0.00)	0.00	-0.10
WASO	<0.01 (-0.01- 0.00)	0.00	-0.18
TST	<0.00 (-0.01- 0.00)	0.00	-0.09
BMI	-0.01* (-0.01 - 0.002)	0.00	-0.23
Amplitude	<0.01 (0.00 - 0.01)	0.00	0.01
Acrophase	0.01 (-0.03 - 0.05)	0.02	0.03

Note. * $p < 0.05$, b= bootstrap coefficient, SE = Standard Error, CI= Bias corrected confidence intervals, β = standardized coefficient, WASO = Wake after sleep onset, TST = Total sleep time, BMI= Body mass index. Includes 95% Bias corrected and accelerated confidence intervals in parentheses. Confidence intervals and standard errors based on 1000 bootstrap samples

3.3.2 Aim 2: Nonparametric Analyses

Nonparametric analyses were completed for all participants and therefore the full sample was used for the nonparametric models (n =109). Figures 12 and 13 illustrate actigraphy data for a single participant with either extreme IV or IS in the SfeRe sample. In regard to covariates, lower IS was significantly associated with being male (r_s = 0.22, p = 0.03), non-Caucasian (r_s = -0.40, p < 0.001), and higher daily average exercise (r_s = -0.22, p = 0.02, Table 25). Additionally, higher IV was significantly associated with being non-Caucasian (r_s = 0.33, p < 0.001) and with unemployment (r_s = -0.28, p < 0.01). Neither IV nor IS were significantly correlated with any of the ImPACT composite scores (Table 27).

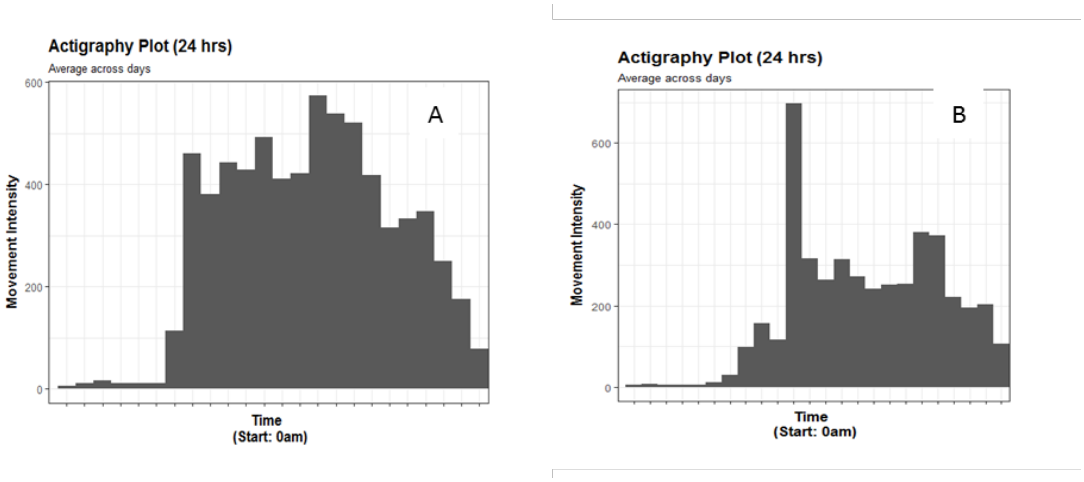

Figure 12. Examples of low and high IV in Study 2. A. Participant who exhibited a low IV (0.46) B. Participant who exhibited a high IV (1.36).

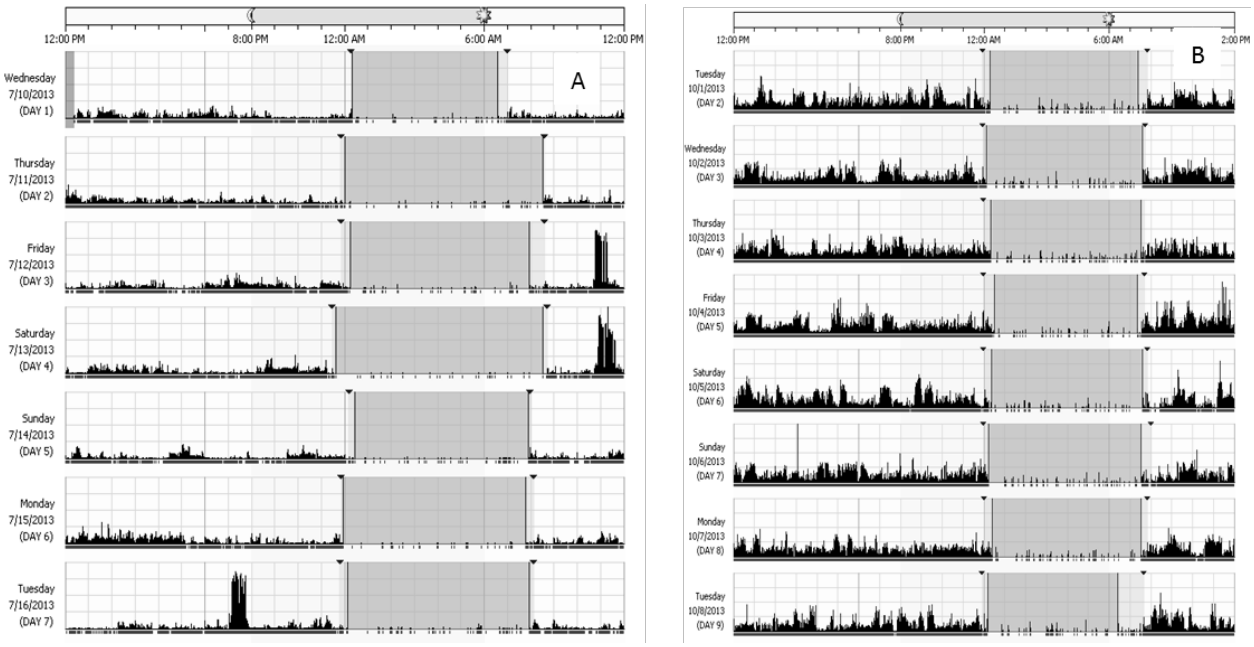

Figure 13. Extreme examples of IS in Study 2. A. Participant who exhibited one of the lower IS (0.28) and B. a participant who exhibited one of the higher IS (0.71) in the sample.

3.3.2.1 Hierarchical regression models

Verbal memory. All of the steps of the models predicting verbal memory were not significant and therefore coefficients were not interpreted.

Visual memory. All of the steps of the models predicting visual memory were not significant and therefore coefficients were not interpreted.

Visual motor speed. The second ($F_{(8,108)} = 2.42$, $R^2 = 0.16$, $p = 0.02$) and third step ($F_{(9,108)} = 2.17$, $R^2 = 0.16$, $p = 0.03$) of the model was significant. ΔR^2 was not significant at any step. Step four of the model was not significant and therefore coefficients from the final step of the model were not interpreted ($F_{(11,108)} = 1.79$, $R^2 = 0.17$, $p = 0.07$).

Reaction time. The model predicting reaction time was significant at step one ($F_{(5,108)} = 2.63$, $R^2 = 0.11$, $p = 0.03$), two ($F_{(8,108)} = 2.18$, $R^2 = 0.15$, $p = 0.04$), three ($F_{(9,108)} = 2.55$, $R^2 = 0.20$, $p = 0.01$) and four ($F_{(11,108)} = 2.25$, $R^2 = 0.20$, $p = 0.02$). ΔR^2 was not significant at any step However, neither of the IS or IV coefficients were significant in the final step of the model (Table 30).

Table 30. Step 4 of robust regression predicting the reaction time composite score

Variable	b (CI)	SE B	Beta
Age	0.01 (0.01-0.02)	<0.01	0.20
Gender	0.01 (-0.03 - 0.05)	0.02	0.07
Race	0.04 (0.00- 0.08)	0.02	0.20
Education	-0.04* (-0.08 - -0.02)	0.02	-0.33
Job Status	<0.01 (-0.03 - 0.02)	0.01	-0.02
Exercise	<0.01 (-0.01- 0.00)	<0.01	-0.12
WASO	<0.01 (-0.01- 0.00)	<0.01	-0.16
TST	<0.01 (-0.01- 0.00)	<0.01	-0.09
BMI	-0.01 (-0.01 - 0.00)	<0.01	-0.20
IS	-0.09 (-0.27 - 0.07)	0.10	-0.11
IV	-0.05 (-0.14 - 0.04)	0.05	-0.13

Note. * $p < 0.05$, b= bootstrap coefficient, SE = Standard Error, CI= Bias corrected confidence intervals, β = standardized coefficient, WASO = Wake after sleep onset, TST = Total sleep time, BMI= Body mass index. Includes 95% Bias corrected and accelerated confidence intervals in parentheses. Confidence intervals and standard errors based on 1000 bootstrap samples

3.3.3 Post Hoc Analyses

3.3.3.1 Models split by gender

In order to determine if there may be different relationships between men and women, correlations and models were run in men and women separately. Table 31 summarizes correlations between RAR measures and composite scores split by gender. There were no significant correlations between RAR measures and composite scores in either gender. Models did not differ greatly from above results and are not reported.

Table 31. Spearman's Correlations with RARs and ImPACT Composite Scores Stratified by Men and Women

	Men				Women			
Variable	Verbal Memory	Visual Memory	Reaction Time	Visual Motor Speed	Verbal Memory	Visual Memory	Reaction Time	Visual Motor Speed
IS	-0.09	0.20	-0.12	-0.12	-0.08	-0.06	-0.14	0.02
IV	-0.08	-0.14	-0.12	0.02	0.03	0.15	-0.08	0.06
Acrophase	-0.10	-0.24	0.08	0.08	0.02	0.19	0.03	0.00
Amplitude	-0.17	0.18	-0.04	-0.20	-0.06	-0.13	0.05	0.01

Note. IS= Interdaily stability, IV= Intradaily variability

3.3.3.2 Models without race

Due to the large impact of race in Study 1, and the association between race and some of the RAR variables in the current sample, race was removed from the model to better understand if race had a significant impact on results. Models did not differ significantly when race was excluded compared to the results summarized above when race was included.

3.3.3.3 Subtests

Because some subtests showed more variation than the composite scores they contributed to, RAR associations with ImPACT subtest scores were explored. Only subtests that exhibited sufficient variation as determined by visual inspection were included in the subtest analyses (Word Memory % Correct, Design Memory % Correct, X and Os % Correct, Three Letters Counted Correct, X O Average Correct Reaction Time, Color Match Average RT). Spearman's correlations revealed a significant association between acrophase and Word Memory % correct (r_s = 0.30, p <0.001; Table 32). However, all robust regression models were not significant predicting each subtest preventing interpretation of coefficients.

Table 32. Spearman's Correlations with RARs and ImPACT Subtests

	Word Memory % Correct	Design Memory % Correct	X and Os % Correct	Three Letters Average Counted Correct	X O Average Correct RT	Color Match Average RT
Acrophase	0.30**	-0.09	0.032	0.01	0.09	0.07
Amplitude	-0.09	-0.08	0.089	-0.09	0.01	-0.07
F	0.04	-0.13	0.112	-0.15	-0.03	0.02
IS	-0.03	0.01	0.133	0.00	-0.03	-0.09
IV	-0.02	0.12	-0.049	0.05	-0.08	-0.02

Note. **$p < 0.01$. IS= Interdaily stability, IV= Intradaily variability

3.3.3.4 RAR comparisons by employed vs unemployed

The differences of RARs by employment status were further investigated using a one-way ANOVA exploring the difference between means for IS, IV, acrophase, and amplitude across employed (part time and full time) vs unemployed/students. Acrophase was significantly earlier in the employed group (M = 15.36, SD = 0.58) relative to the unemployed/student group (M = 15.70, SD = 0.60; $F_{(1,107)}$ = 8.98, p < 0.01; Figure 14A). In addition, fragmentation differed across groups such that those that were unemployed (M = 0.92, SD = 0.22) had higher fragmentation relative to those who were employed (M = 0.78, SD = 0.21; $F_{(1,107)}$ = 11.66, p < 0.01; Figure 14B). The same Spearman's correlations and hierarchical regression models as primary analyses stratified by job type were completed and revealed no significant associations between RAR measures and composite scores, likely due to small sample sizes.

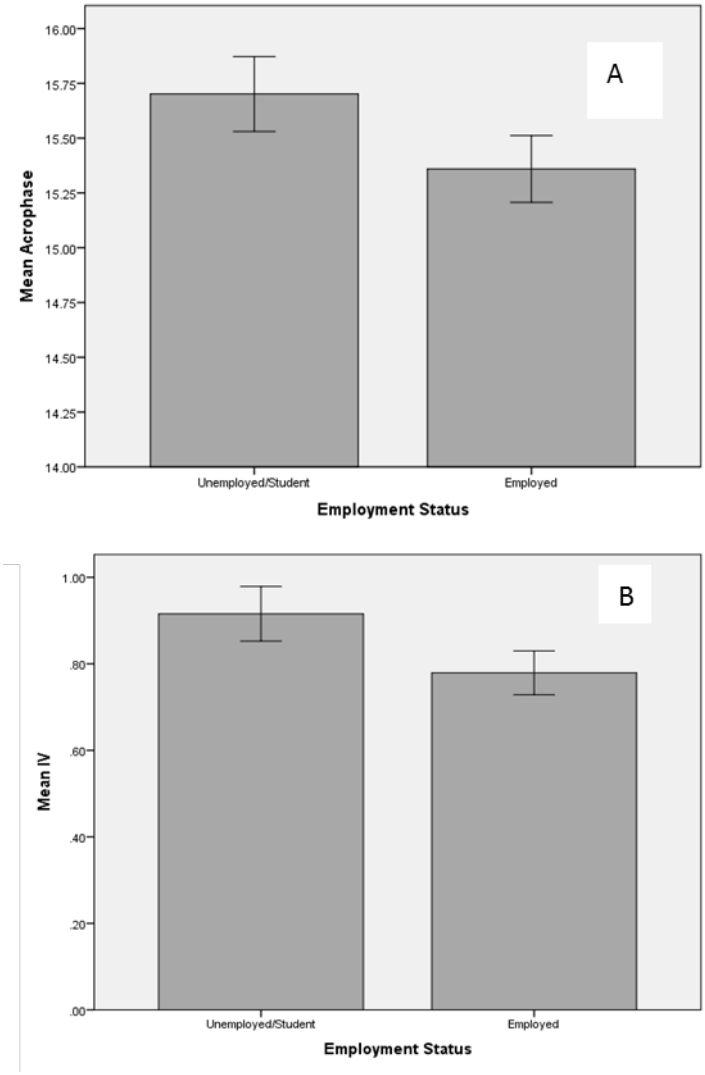

Figure 14. Mean acrophase (A) and IV (B) by employed and unemployed/student group. Both depict significant differences. Error bars represent +/- two standard errors.

3.1 DISCUSSION

The aim of the second study was to test an association between RAR measures with cognitive performance in a young adult sample. Hypotheses predicted that individuals with more delayed acrophases, lower amplitudes, higher fragmentation, and lower stability would exhibit poorer performance on the reaction time, visual motor speed, and visual memory composite scores relative to those with earlier acrophase, more robust amplitudes, less fragmentation and higher RAR stability. However, results indicated that there was no association between RAR measures and composites scores, failing to support study predictions.

3.1.1 Lack of Relationships Between RARs and Composite Scores

The lack of support for Study 2 hypotheses may be explained by several factors. First, ImPACT did not capture sufficient variation in cognitive performance in this sample. ImPACT was used in the current study due to its ease of computerized administration and lower participant burden relative to longer traditional neuropsychological batteries. Further, ImPACT subtest norms with baseline, pre-concussion data in high school and college athletes (ages 13- 21) have been published suggesting sufficient variation in subtest scores (Henry & Sandel, 2014). However, the skewed performance towards the ceiling or maximum scores, especially verbal memory and visual motor speed composite scores (Figure 13), in the current sample indicated that the slightly older age of our sample (18 to 30 years) and the inclusion of a mix of participants beyond athletes may have created a sample that was able to “out-perform” some of the subtests. The negative skew of outcome data made investigating associations with the composite scores difficult as it truncates the variation to be predicted by variables of interest (i.e., RAR measures)

and creates a non-normal distribution of outcome variables. Interestingly, testing time in the individuals who had accurate time stamps on ImPACT suggested that participants were completing cognitive testing during what was likely the descending limb of the circadian rhythm in alertness (Wright et al., 2002; Dijk et al., 1992), which would theoretically have led to a larger variation in performance than observed. The current null results may be due to the overrepresentation of high scores in the SFeRe sample, or a ceiling effect.

Second, the exclusion of irregular sleep/wake schedules and extreme chronotypes may have restricted variance in both RARs and ImPACT scores in the SFeRe sample. Originally, the sample was considered to have sufficient variance in circadian variables due to the normal distribution of self-reported chronotype. Further, although participants were excluded if they showed variation in their sleep/wake times, variation in RARs was still expected. This was supported by the relatively similar standard deviations in the nonparametric measures in Study 1 (IV *SD* = 0.21; IS *SD* = 0.17) and Study 2 (IV *SD* = 0.22; IS *SD* = 0.11). However, lower variation in both amplitude and acrophase in Study 2 (amplitude *SD* = 44.52; acrophase *SD*= 0:37) relative to Study 1 (amplitude *SD* = 78.62; acrophase *SD*= 1:08), may indicate that the extended cosine RAR measures were likely restricted in Study 2 and this may have reduced our ability to find associations with these measures and ImPACT scores. Similarly, if RAR measures are indeed related to cognitive performance, restricting RAR variance with strict inclusion and exclusion criteria may explain the lack of significant associations.

In addition, explanations for null results that are shared with Study 1 are further described in the General Discussion (pg. 86). These explanations include a lack of RAR associations in younger samples relative to older samples, in which the relationship has been substantiated, and

the possibility that circadian disruption may not impact cognition in young adults. Further, the limitation section below outlines additional explanations.

3.1.2 Potential Masking of RARs by Employment

Due to the hypotheses developed from the Study 1 results that RARs may be vulnerable to masking, the influence of employment on RARs was explored further in Study 2. Although the current sample did not collect type of job for those employed, making it difficult to discuss how the type of job may impact RARs, we were able to explore how RARs may differ by employment and unemployment. First, *post hoc* analyses revealed that acrophase and fragmentation significantly differed by job status. Acrophase was earlier amongst those who were employed full time compared to those who reported being unemployed. Further, individuals who were unemployed had significantly higher fragmentation than those who were employed full time. This is consistent with Luik et al., (2013), who found that individuals who were employed exhibited higher fragmentation relative to those who were unemployed. Although we are unable to directly test this in the current study, it may be that students and the unemployed are more able to tailor their daily routines to match their internal circadian rhythms, staying active and going to sleep later (i.e., later acrophase), due to not needing to rise early to go to work at a predetermined time in the morning. Additionally, individuals in this group, especially students, are likely transitioning from sitting in classes to walking around campus several times a day, which would increase daily RAR fragmentation by alternating between periods of inactivity and relatively higher activity (i.e., rushing to the next class). Together, this suggests that students and those who are unemployed may have differences in RAR measures

that are not due to disruption in the circadian system, but are rather due to masking by sedentary job or student status.

The unemployment/student group in the current sample provided an opportunity to further explore the conclusion from Study 1 that RARs may be masked by job. Specifically, relationships between RARs and cognition could be tested without the potential confound of job. However, both correlations and regression models investigating the relationship between RARs and ImPACT composite scores were not significant. This was likely due to the small sample size of unemployed individuals (n = 50), and the lack of variation in most of the ImPACT composite scores discussed above. Further research investigating the relationship between RARs and cognition should include, or be restricted to unemployed groups, or use only non-work days, to better parse the impact of employment on RARs.

3.1.3 Summary

Study hypotheses that both extended cosine and nonparametric RARs would be associated with ImPACT composite scores were not supported. Further, in contrast with Study 1, no association was found between RAR measures and verbal memory. The lack of findings was likely due to both due to the tendency for participants to perform well on the ImPACT and the likely restriction of RAR measures by study exclusion criteria.

3.1.4 Study Limitations and Strengths

Study 2 included several strengths. The SFeRe study included a relatively large sample of healthy young adults with measures of both actigraphy and cognition. The sample included a

sufficient amount of days of actigraphy to measure RARs accurately. Further, the study included a cognitive measure that occurred directly following the actigraphy collection period, allowing for proximal associations between RARs and cognitive performance to be tested. In sum, the SFeRe study offered the rare ability to investigate circadian measures and cognition in a large, healthy young adult sample.

In addition to the lack of variation in ImPACT and some RAR measures, Study 2 also included additional limitations. First, we were unable to control for time of testing due to a technical problem in saving testing time. The lack of the covariate may have influenced are ability to detect an association between RARs and subtests in this sample. However, time of testing in Study 1 did not significantly predict any of the cognitive factors or subtests, indicating that likely would not have greatly changed results. Further, among the 69 participants who had time of testing available in the current sample, there was no association with ImPACT composites scores, indicating that time of testing may not contribute significantly to performance on ImPACT in this sample.

Similar to Study 1, Study 2 was a cross-sectional, observational study. If results would have revealed significant associations between RARs and ImPACT scores, we would have been unable to determine direction of the associations. Further, because Study 2 did not directly manipulate RARs while limiting additional confounding variables (e.g., job or social interaction), we would have been limited in our ability to make conclusions that changes in RARs cause changes cognition.

3.1.5 Future Directions

In order to better understand how RARs may impact cognition in younger samples, two study design factors should be modified from the current study protocol. First, future research designed to test RARs and cognition should not exclude individuals who exhibit variation in sleep timing so that a full range of RARs is represented. Second, a full neuropsychological exam, similar to that of Study 1, would be ideal in order to capture sample variation in cognitive functioning by using neuropsychological tests that are not vulnerable to ceiling effects in healthy young adults.

In addition, future research could focus on further parsing the potential effect of environmental influences on RARs that may ultimately mask circadian variation. It would be interesting to compare melatonin rhythms, the gold standard of circadian timing, and RARs in this age group to quantify how much RARs vary from the gold standard circadian marker. Further, it would be interesting to explore how job-related activity, student status, social interactions, and other environmental influences not previously studied in the RAR literature may covary with difference in the RAR and DLMO measures, offering a glimpse at not only the differences between a known circadian rhythm and RARs in this sample, but also a better understanding of whether masking of amplitude by midday activity may be occurring in the working-age population. The current age range would be ideal for this study because it would likely include unemployed individuals as well as students, who may be more likely to choose their own schedules, as well as individuals in part time and full-time jobs, to capture the full range of potential job-related influences.

3.1.6 Conclusions

Study 2 was performed in order to better understand how RARs in young adult samples might be associated with cognition. Specifically, it was predicted that delayed, blunted, fragmented, and unstable rhythms would be associated with lower scores on visual memory, visual motor speed, and reaction time scores of the ImPACT. In contrast with predictions, no significant associations were found in the young adult sample between RAR measures and cognitive scores. This was likely due to the ceiling effect on ImPACT scores and the restricted range in RAR measures. In continuation of the hypothesis suggested by Study 1 that employment may influence the way individuals exhibit RARs, those who were students or unemployed had significantly different RARs than those who were employed (Part time or full time). Again, environmental influences that are age-dependent may affect how RARs are exhibited in individuals. Further research is required to better understand both the impact of non-circadian variables on RARs and the impact of circadian disruption in a young adult sample.

4.0 GENDERAL DISCUSSION

The overarching goal of the current series of studies was to investigate the relationship between circadian disruption and cognition in healthy middle-aged and young adult samples by using RARs as proxy for circadian functioning. It was predicted in both studies that more delayed, blunted, fragmented, and unstable rhythms would be associated with poorer performance in the domains of processing speed, reaction time, visual spatial memory, executive functioning, and working memory. However, hypotheses were not supported in either study. Instead, a surprising finding linked lower RAR amplitude with better performance in the verbal proficiency domain in the middle-aged sample. This finding was not predicted as verbal proficiency is thought to be a stable trait and should theoretically not be affected by circadian rhythms. *Post hoc* mediation analyses suggest that job type, and perhaps sedentary job-related behavior, partially explains the relationship between RAR measures and verbal proficiency, indicating that non-circadian related environmental influences likely obscured our ability to measure the circadian portion of RARs in this sample. Further supporting this idea, Study 2 analyses suggested that RARs differed between the employed and unemployed groups. Together, the results did not support study hypotheses though they may highlight potential confounding factors that masked circadian driven RAR activity in this sample. The potential impact of job may call into question whether RARs in working samples accurately reflect circadian functioning and may also explain study null results.

Results from Study 1 extend the current literature in older adults and implicate a relationship between WASO and predicted cognitive factors of processing speed, reaction time, visual spatial memory, executive functioning, and working memory in middle-aged adults. Given that increased WASO is likely a result of the interaction of decreased sleep drive, circadian disruption, and other factors (i.e., depression, physical activity, gender), and that WASO is likely less vulnerable to being masked by sedentary job-related behavior, it may be that WASO can provide an interesting way to investigate the interaction of sleep and circadian functioning on cognition in the future. Further studies may help elucidate both the circadian contribution to WASO and how that effect may impact cognitive performance in middle-aged and young adults.

4.1.1 Alternative Explanations for Null Results

4.1.1.1 Study Limitations

In addition to null results potentially being driven by a masking of RARs by job-related sedentary behavior, another potential reason for the lack of associations between RARs and cognitive domains may be the study limitations highlighted above. For instance, the AHAB II sample provided a rare opportunity to compare actigraphy measures and cognition in a previously measured large healthy middle-aged sample. However, the duration between actigraphy and cognitive assessment varied greatly by person, and although we have some reason to believe that this did not affect results, it cannot be ruled out. In addition, Study 2 used the ImPACT measures for cognition. This particular measure was used in the SFeRE study because of its brief and convenient administration, though inspection of the data following collection revealed that it may be insensitive to cognitive changes in healthy young adults. The lack of variation seen in Study 2 ImPACT composite scores may have prevented the detection of a

relationship between RARs and cognition in a young sample. Lastly, because original study hypotheses included testing whether the impact of RARs on cognition changed over individual age, analyses included neuropsychological tests, which were not normalized by age, gender, or years of education. Given the large impact of gender and years of education on the results, remaining variance in cognitive variables unexplained by these demographic covariates may have been limited and therefore attenuated our ability to detect results. Overall, the null results may have been due to using samples of convenience that were not designed to test the current study hypotheses and may be partially due to the lack of correcting individual neuropsychological scores prior to analyses.

4.1.1.2 RARs are Only Related to Cognition in Older Samples

It is also possible that RARs are not associated with cognition in young and middle-aged populations. This lack of impact on cognitive functioning in this age range may be due to either the masking of circadian variation in RARs in younger samples or may reflect the absence of an effect of RARs on cognition until older age. First, it may be that potential masking factors are not present in older age, allowing older individuals to exhibit RARs that more accurately reflect their circadian functioning. Indeed, preliminary evidence in Study 1 and 2 suggests a potential masking of RARs by job-related sedentary behavior, which would be removed following retirement. Therefore, it is possible that the influence of internally driven circadian rhythms (as indexed by RARs) on cognition may be masked by externally-imposed schedules, and becomes evident only once an individual leaves the workforce and is free to engage in behavior on a self-determined schedule. Taken together, individuals may experience dynamic changes in

environmental influences (e.g., job) on RARs, which may explain age-related variation in the impact of RARs on cognition.

Second, it may be that the impact of circadian disruption and aberrant RARs on cognition may grow over time. Aging has been associated with a gradual changes in circadian functioning that ultimately result in lower amplitudes, shorter phases, internal desynchronization of peripheral clock mechanisms (e.g., Dijk, Duffy, Riel, Shanahan, & Czeisler, 1999; Münch et al., 2005; Tozawa et al., 2003; Van Cauter, Leproult, & Kupfer, 1996; Yamazaki et al., 2002; for review see Duffy, Zitting, & Chinoy, 2015) and potentially abnormal patterns of clock gene expression in the brain (Chen et al., 2016), which may translate to overall decline in cognitive functioning. This is consistent with the finding that age interacts with RAR fragmentation to impact cognitive performance in a group of 45 to 98 years old (Luik et al., 2015), such that middle-aged adults were less impacted by fragmentation. Further, our findings suggest smaller effect sizes of RARs on subtest performance relative to what has been observed in elderly samples, indicating a smaller impact of RARs on cognition in younger samples. These results may indicate that progressive age-related changes in circadian functioning translate to a growing impact on cognition over time. In sum, the lack of findings in the current sample may be a result of an attenuated impact of circadian disruption and aberrant RARs on cognition in younger samples that may increase in older age.

4.1.1.3 Individual Circadian Variation is not Related to Cognition

If RARs indeed represent circadian functioning in the current sample, the null results may be due to the overall lack of association between circadian variation and cognition. Although this is possible, it is inconsistent with the current animal literature that suggests that circadian disruption changes brain morphology in the hippocampus and prefrontal cortex and is related to

poor performance on cognitive tasks (Craig et al., 2008; Karatsoreos et al., 2011; Zelinski et al., 2014). It is also inconsistent with human studies that suggest that shift workers and those that experience social jet lag also exhibit lower cognitive performance relative to those who do not (e.g., Åkerstedt, 1998; Ansiau et al., 2008; Haraszti et al., 2014). Further, it is inconsistent with the human literature, which suggests that forced disruption of circadian rhythms impacts cognition and there is a circadian variation to cognition throughout the day (Burke et al., 2015; Darwent et al., 2010; Dijk et al., 1992; Silvia et al., 2010; Santhi et al., 2016; Wyatt et al., 1999; Wright et al., 2002; Zhou et al., 2011). Ultimately, however, further investigation using more direct measures of circadian functioning will be required to better understand the potential association between circadian disruption and cognition, and to best handle the potential of masking midday activity.

4.1.2 Future Directions

In addition to developing study designs described above to better understand how RARs may be masked by age-related environmental influences, future research should focus on understanding the relationship of circadian variables and cognition. The current series of studies aimed to better understand how natural circadian variation may impact middle-aged and young adults, a topic that has remained mostly understudied. However, due to the possibility that RARs were not an accurate proxy for circadian functioning in these groups, further research should be developed to better understand the impact of circadian variation, in order to provide targets for improving both normative and pathological cognition. Novel lines of research could aim to capture other known markers of circadian variation including DLMO or midsleep. It would be interesting to then link these with neuropsychological functioning to elucidate potential relationships between delayed

rhythms and lower cognitive functioning. Although one study has attempted to relate DLMO with IQ testing in a small group of adult males (Waller et al., 2016), broadening this research design with repeated measures, and by including a larger sample, including both genders, and a larger neuropsychological battery exploring cognitive domains like processing speed and executive functioning will be important.

In order to further explore differences between the current study findings and those in the elderly, longitudinal studies will be helpful in further discerning the interplay of RARs, circadian functioning, and cognition. For instance, research designs that quantify changes in RARs and circadian variables before and after retirement may help discern if RARs are a better reflection of circadian functioning after retirement than during working years. In addition, follow-up longitudinal RAR collection in those participants from Study 1 that were driving the RAR and subtest associations would be important to investigate whether those individuals experience a magnification of the impact of RARs over time. Results consistent with these predictions support that RARs, and perhaps circadian functioning, become increasingly impactful on cognition over the aging process. Together, longitudinal collection of RARs and circadian markers that are thought to be less influenced by the environment (i.e., DLMO) in concert with a robust neuropsychological battery will provide important insight on the impact of circadian variation and RARs on cognitive functioning across development.

Another approach to consider in future studies would be that of a circadian intervention that could directly test our hypothesized model. If circadian desynchrony is mechanistic in cognitive functioning, then interventions that regularize circadian timing, consolidate sleep to minimize WASO, or even advance delayed rhythms would be hypothesized to lead to better cognitive functioning. These interventions may include bright light therapy or interventions

which target sleep. For instance, Cognitive Behavioral Therapy for Insomnia (CBT-I) have been shown to decrease WASO in older adults, has been correlated with improvement in cognition (Wilckens et al., 2017), and may provide a way of experimentally manipulating circadian rhythms in young and middle-aged adults. If improved behaviors consistent with these treatments (i.e., consolidation of sleep, advanced or stabilized rhythms) can improve cognition in midlife, the greater burden and expense of longitudinal studies would not be required.

4.1.3 Impact on Current Literature

In a review of the RAR literature, beyond those studies linking RARs and cognition, a majority of studies refer to RARs a representation of circadian functioning (for review see Goncalves et al.,2014). Further, a subset of these collect RARs in middle-aged and young adult samples (e.g., Berger et al., 2010; Berle, et al., 2010; Dhruva et la., 2012; Hare, Jones, Evershed, 2006; Huang et al., 2002; Jones et al., 2005; Levin et al., 2005; Savard et al., 2009; Van Veen et al., 2010), but do not collect job type information. Evidence from the current study suggest that RARs may potentially be masked by environmental influences that affect this age group more than in older adults. Therefore, it may be that associations with RARs may be a result of environmental influences instead of the circadian variation claimed in the papers. For example, the changes in amplitude of RARs in individual before and after chemotherapy in breast cancer patients may not be due to changes in circadian rhythms as a result of treatment, as hypothesized by the authors, and may instead be due to changes in environmental influences (e.g., inability to work during the treatment period; Savard et al., 2009). Or, the environmental influence of RARs may explain the large amount of null associations in some papers (Berger et al., 2010). In addition, differences between control groups and those with cognitive pathologies that occur in middle-age (e.g., 147

schizophrenia; Berle, et al., 2010) may be a result of differences in employment, for example, more so than differences in circadian functioning. If further research suggests that environmental influences, like job, mask the portion of RARs driven by the circadian system in middle-aged and young adults, the incorporation of sedentary midday behavior as covariates in future research investigating RARs in this age range will be imperative in order to extract the desired information about the impact of circadian functioning outcomes of interest.

4.1.4 Conclusion

In summary, the prediction of both studies that RARs would be associated with specific cognitive domains in middle-aged and young-adults was generally not supported. Instead, preliminary evidence may suggest that RARs are not an accurate proxy of circadian functioning in this age range and are influenced by environmental factors that create sedentary behavior like job. This represents an important area of further research, as the potential masking effects may influence interpretation of RAR studies specifically in middle-aged and young adults. Further, results may suggest that RARs do not impact cognition until older age, perhaps due to the unmasking of RARs by job following retirement, or gradual increased impact of circadian variation over the aging process. In contrast, preliminary relationships between WASO and cognitive factors may implicate the importance of proper circadian and sleep drive alignment and introduce an interesting line of research in middle-aged adults. Overall, the findings from the current study produce additional lines of research to both better understand the true impact of the circadian system on RARs in middle-aged and young adults as well as to develop improved ways of investigating the impact of circadian variation in normative cognitive functioning.

APPENDIX A

ORIGINALLY PROPOSED COVARIATES

A.1 STUDY 1: METHODS AND RESULTS

The original proposal included the covariates described in Table A1. Analyses using these covariates are included here for completeness. Hierarchical regression models were run for each cognitive factor. Table A2 summarizes results for the extended cosine approach. Importantly, neither amplitude nor acrophase were significantly associated any of the cognitive composite scores. Table A3 summarizes the results for the nonparametric modes. IS was not significantly associated with any of the composite scores. IV was significantly associated with verbal proficiency above and beyond study covariates ($F_{(11,401)}$ =17.55, R^2 = 0.33, $p < 0.001$, $\beta = 0.11$, $p = 0.019$). These results mirror those of the analyses that excluded race as a covariate, such that more fragmentation of RARs was associated with higher verbal proficiency scores.

Table 33. Proposed covariates for extended cosine and nonparametric models

Blocks	Aim 1a and Aim 2a: Cosinor Analysis	Aim 1b and 2b: Nonparametric Analysis
1: Demographic	Age Gender Education Time of Testing	Age Gender Education Time of Testing
2: Sleep and Health Factors	Body Mass Index Mood Variable Weekly Alcohol WASO TST	Body Mass Index Mood Variable Alcohol Intake WASO TST
3: RAR variables	Amplitude Acrophase Pseudo *F*	Interdaily stability Intradaily variability

Note. CES-D = The Center of Epidemiological Studies Depression Scale, PHQ-9= Patient Health Questionaire-9, WASO= Wake after sleep onset, TST= Total sleep time

Table 34. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Extended Cosine Analyses For Cognitive Factors

Variable	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.03 (-0.25)***	-0.03 (-0.27)***	-0.03 (-0.22)***	-0.03 (-0.26)***	-0.03 (-0.25)***	-0.01 (-0.07)
	0.01	0.01	0.01	0.01	0.01	0.01
Gender	-0.24 (-0.13)	-0.20 (-0.11)*	0.04 (0.02)	-0.13 (-0.08)	-0.16 (-0.09)	-0.16 (-0.09)*
	0.09	0.09	0.09	0.08	0.08	0.08
Testing Time	<0.01 (0.02)	<0.01 (-0.04)	<0.01 (-0.02)	<0.01 (-0.05)	<0.01 (-0.03)	<0.01 (0.02)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Years of School	0.10 (0.32)***	0.09 (0.27)***	0.10 (0.31)***	0.09 (0.26)***	0.09 (0.28)***	0.15 (0.47)***
	0.02	0.02	0.02	0.02	0.02	0.01
WASO	-0.01(-0.12)**	-0.01 (-0.12)*	<0.01 (-0.06)	-0.01 (-0.11)*	-0.01 (-0.12)*	0.01 (-0.10)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
TST	<0.01 (0.05)	<0.01 (0.05)	<0.01 (0.07)	<0.01 (0.07)	<0.01 (0.07)	<0.01 (0.02)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI	-0.02(-0.11)*	-0.01 (-0.08)	-0.01 (-0.05)	-0.01 (-0.08)	-0.01 (-0.07)	-0.02 (-0.10)*
	0.01	0.01	0.01	0.02	0.02	0.01
CES-D	-0.20(-0.08)	-0.21 (-0.09)*	-0.23 (-0.10)*	-0.20 (-0.09)	-0.21 (-0.09)*	-0.14 (-0.06)
	0.11	0.11	0.11	0.11	0.11	0.10
Weekly Alcohol	0.02 (0.09)*	0.02 (0.11)*	0.03 (0.12)*	0.03 (0.13)**	0.02 (0.12)**	0.02 (0.09)*
	0.01	0.01	0.01	0.01	0.01	0.01
Amplitude	-0.04(-0.02)	-0.02 (-0.01)	-0.02 (-0.02)	-0.02 (-0.01)	-0.01 (-0.01)	-0.11 (-0.07)
	0.08	0.08	0.08	0.08	0.08	0.07
Acrophase	-0.02(-0.02)	-0.03 (-0.03)	-0.03 (-0.03)	-0.02 (-0.03)	-0.02 (-0.02)	-0.01 (-0.01)
	0.04	0.04	0.04	0.04	0.04	0.04
ΔR^2	0.001	0.001	0.001	0.001	0.08	0.004
Model *p* value	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset, CES-D = Center for epidemiologic studies- depression scale, *** p <0.001, ** p< 0.01, *p<0.05

Table 35. Model Unstandardized Coefficients (Standardized Coefficients) for the Fourth Step of Nonparametric Analyses For Cognitive Factors

Variable	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Age	-0.03 (-0.24)***	-0.03 (-0.27)***	-0.03 (-0.21)***	-0.03 (-0.26)***	-0.03 (-0.25)***	-0.01 (-0.06)
	0.01	0.01	0.01	0.01	0.01	0.01
Gender	-0.25 (-0.13)**	-0.20 (-0.11)*	0.04 (0.02)	-0.13 (-0.08)	-0.16 (-0.09)	-0.16 (-0.09)*
	0.08	0.09	0.09	0.08	0.08	0.08
Testing Time	<0.01 (-0.01)	<0.01 (-0.04)	<0.01 (-0.03)	<0.01 (-0.04)	<0.01 (-0.02)	<0.01 (0.02)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Years of School	0.11 (0.32)***	0.09 (0.27)***	0.09 (0.29)***	0.09 (0.28)***	0.09 (0.28)***	0.14 (0.45)***
	0.02	0.02	0.02	0.02	0.02	0.01
WASO	-0.01 (-0.12)**	-0.01 (-0.12)*	<0.01 (-0.06)	-0.01 (-0.11)*	-0.01 (-0.12)*	<0.01 (-0.08)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
TST	<0.01 (0.05)	<0.01 (0.05)	<0.01 (0.07)	<0.01 (0.06)	<0.01 (0.06)	<0.01 (0.03)
	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
BMI	-0.02 (-0.11)*	-0.01 (-0.07)	-0.01 (-0.05)	-0.01 (-0.08)	-0.01 (-0.07)	-0.02 (-0.10)*
	0.01	0.02	0.01	0.01	0.01	0.01
CES-D	-0.19 (-0.08)	-0.21 (-0.09)*	-0.22 (-0.10)*	-0.19 (-0.09)	-0.20 (-0.09)*	-0.12 (-0.05)
	0.11	0.11	0.11	0.11	0.11	0.10
Weekly Alcohol	0.02 (0.09)*	0.02 (0.11)*	0.03 (0.12)**	0.03 (0.13)**	0.03 (0.12)**	0.02 (0.09)*
	0.01	0.01	0.01	0.01	0.01	0.01
IS	0.27 (0.05)	0.22 (0.04)	0.19 (0.04)	0.22 (0.04)	0.20 (0.04)	0.27 (0.05)
	0.25	0.26	0.26	0.25	0.25	0.24
IV	0.08 (0.02)	0.02 (0.01)	0.37 (0.09)	0.06 (0.02)	0.08 (0.02)	0.46 (0.11)*
	0.21	0.21	0.21	0.21	0.21	0.20
ΔR^2	0.002	0.001	0.006	0.002	0.001	0.01
Model *p* value	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

Note: Standard errors listed under coefficients. All statistics are taken from the fourth step of the regression models. BMI = body mass index, TST= Total sleep time, WASO= wake after sleep onset, CES-D = Center for epidemiologic studies- depression scale, IV= intradaily variability, IS = interdaily stability *** p <0.001, ** p< 0.01, *p<0.05

A.2 STUDY 2: METHODS AND RESULTS

Again, original covariates are summarized in Table A1. Robust regression utilizing 95% bias corrected and accelerated confidence intervals due to non-normally distributed residuals of OLS regression models (Fields, 2012). For the extended cosine models predicting visual memory, verbal memory and visual motor speed were not significant at any of the included steps, and therefore the coefficients were not interpreted. In contrast, the second ($F_{(8,107)}$ =2.75, R^2 = 0.18, $p < 0.009$) and third step ($F_{(10,107)}$ = 2.21, R^2 = 0.19, p = 0.02) of the regression model predicting reaction time was significant. In the third step, neither amplitude nor acrophase was significantly associated with reaction time scores above and beyond study covariates (Table A4). Similarly, for the nonparametric models, visual memory, verbal memory and visual motor speed were not significant at any of the included steps, and therefore the coefficients were not interpreted. The second ($F_{(8,108)}$ = 2.47, R^2 = 0.18, p = 0.02) and third step ($F_{(10,108)}$ = 2.10, R^2 = 0.18, p = 0.03) predicting reaction time was again significant. In the third step, neither IV or IS were significantly associated with reaction time above and beyond study covariates (Table A5). These results are similar to main analyses which suggest that there was no association between RAR measures and ImPACT composite scores.

Table 36. Third step of extended cosine model predicting reaction time composite score

Variable	b (CI)	SE B	β
Age	0.01 (00.00-0.02)	0.01	0.24
Sex	0.01 (-0.03-0.05)	0.02	0.07
Education	-0.04* (-0.07-0.00)	0.02	-0.32
WASO	0.00* (0.00)	0.00	-0.23
TST	0.00 (0.00-0.00)	0.00	-0.11
BMI	-0.01* (-0.01-0.00)	0.00	-0.25
PHQ9	0.00 (-0.02-0.03)	0.01	0.02
Alcohol	-0.04 (-0.09-0.01)	0.02	-0.18
Amplitude	0.00 (0.00-0.00)	0.00	-0.02
Acrophase	0.01 (-0.02-0.04)	0.02	0.06

Note. * $p < 0.05$, SE = Standard Error, CI= Confidence Intervals, WASO = Wake after sleep onset, TST = Total sleep time, BMI= Body mass index. PHQ9= Patient Health Questionare-9. Includes 95% Bias corrected and accelerated confidence intervals in parentheses. Confidence intervals and standard errors based on 1000 bootstrap samples

Table 37. Third step of nonparametric model predicting reaction time composite score

Variable	b (CI)	SE B	β
Age	0.01 (0.00-0.02)	0.01	0.24
Sex	0.01 (-0.03-0.05)	0.02	0.07
Education	-0.04* (-0.08—0.01)	0.02	-0.32
WASO	0.00* (<0.01-<0.01)	0.00	-0.20
TST	0.00 (0.00-0.00)	0.00	-0.10
BMI	-0.01 (-0.01-0.00)	0.00	-0.21
PHQ9	0.00 (-0.02-0.03)	0.01	0.01
Alcohol	-0.04 (-0.08-0.01)	0.02	-0.17
IS	-0.10 (-0.27-0.05)	0.09	-0.12
IV	-0.03 (-0.13-0.07)	0.05	-0.07

Note. * $p < 0.05$, SE = Standard Error, CI= Confidence Intervals, WASO = Wake after sleep onset, TST = Total sleep time, BMI= Body mass index. PHQ9= Patient Health Questionare-9. Includes 95% Bias corrected and accelerated confidence intervals in parentheses. Confidence intervals and standard errors based on 1000 bootstrap samples

APPENDIX B

PSEUDO F STATISTIC RESULTS

B.1 STUDY 1: METHODS AND RESULTS

Due to the high correlation between the F statistic and amplitude, the two could not be in the same regression model. Therefore, additional models were created with the same four steps as preliminary analyses. However, in the fourth step, F was added in replacement of amplitude and acrophase.

First 3 steps in all analyses replicated previous analyses. The fourth step model was significant in the model predicting visual spatial reasoning ($F_{(13,\ 397)}$ = 20.87, R^2 = 0.41, p <0.001), though the F coefficient was not significant (β = -0.05, p = 0.23). The fourth step model was significant in the model predicting working memory ($F_{(13,\ 397)}$ = 16.84, R^2 = 0.36, p <0.001), though the F coefficient was not significant (β = -0.04, p = 0.36). The fourth step model was significant in the model predicting verbal learning ($F_{(13,\ 397)}$ = 10.98, R^2 = 0.27, p <0.001), though the F coefficient was not significant (β = -0.04, p = 0.40). The fourth step model was significant in the model predicting executive functioning ($F_{(13,\ 397)}$ = 17.51, R^2 = 0.37, p <0.001), though the F coefficient was not significant (β = -0.04, p = 0.31). The fourth step model was significant in the model predicting processing speed ($F_{(13,\ 397)}$ = 17.29, R^2 = 0.37, p <0.001), though the F

coefficient was not significant (β = -0.04, p = 0.34). The fourth step model was significant in the model predicting verbal fluency ($F_{(13, 397)}$ = 23.46, R^2 = 0.44, p <0.001), though the F coefficient was not significant (β = -0.06, p = 0.18). In summary, the F statistic was not significant in any of the cognitive factor models.

B.2 STUDY 2: METHODS AND RESULTS

Again, the F statistic was highly correlated with amplitude and therefore was unable to be included in any of the models due to multicollinearity. Therefore, separate robust regression models were built with the F statistic in the fourth step.

Similar to primary analyses, no steps of the models predicting verbal and visual memory composite scores were significant and therefore the coefficients of the models were not interpreted. The first, second, third, and fourth step were significant in the model predicting visual motor speed ($F_{(10,107)}$ = 2.49, R^2 = 0.11, p = 0.04, $F_{(10,107)}$ = 2.34, ΔR^2 =0.05, p = 0.02, $F_{(10,107)}$ = 2.07, ΔR^2 <0.01, p =0.04, $F_{(10,107)}$ = 2.38, ΔR^2 = 0.04, p = 0.02, respectively). However, the F coefficient was not significant (b = -0.01, SE = 0.01, CI = -0.01-0.00, p = 0.06). The first, second, third, and fourth step were significant in the model predicting reaction time ($F_{(10,107)}$ = 2.67, R^2 = 0.12, p = 0.03, $F_{(10,107)}$ = 2.14, ΔR^2 = 0.03, p = 0.04, $F_{(10,107)}$ = 2.71, ΔR^2 = 0.05, p = 0.01, $F_{(10,107)}$ = 2.45, ΔR^2 = 0.01, p = 0.01, respectively). However, the F coefficient was not significant (b = -0.01, SE = 0.01, CI = -0.01 - 0.01, p = 0.58). In summary, the F coefficient was not significant in any of the ImPACT composite score models.

APPENDIX C

CARDIOVASCULAR VARIABLES

In order to understand how cardiovascular variables impact both RARs and cognition, blood pressure, standard total cholesterol, high-density lipoprotein, cholesterol, triglycerides, glucose, insulin measures were included in RAR and cognition analyses.

Blood pressure was averaged over two recordings following a 10 minute rest period. Blood draws were collected after a 12 hour fast. Blood samples were used to determine standard total cholesterol, high-density lipoprotein, cholesterol, triglycerides, glucose, insulin concentrations. Insulin resistance was estimated by the homeostatic model of insulin resistance (HOMA-IR). Due to skew, triglycerides, insulin, glucose and HOMA-IR were log transformed. Pearson's correlations were completed (Table 1C). The variables were then entered into an additional step of primary hierarchical regression analyses.

Extended cosine models included 397 participants while nonparametric models included 401 participants. The models did not differ from primary analyses such that amplitude (β = -0.13, p <0.001, $F_{(22,396)}$ = 16.34, R^2 = 0.49, p < 0.001) and IV (β = 0.18, p <0.01, $F_{(18,400)}$ = 15.79, R^2 = 0.48, p < 0.001) both were significantly associated with verbal proficiency. No other

RAR measures were significantly associated with cognition following correction for cardiovascular variables.

Table 38. Cardiovascular correlations with RARs and cognitive factors.

Variables	Amplitude	Acrophase	IS	IV	Visual Spatial Reasoning	Working Memory	Verbal Learning	Executive Functioning	Processing Speed	Verbal Proficiency
Total Cholesterol (mg/dl)	-0.08	-0.02	0.05	-0.09	-.128*	-.137**	-.123*	-.115*	-.125*	-0.06
HDL (mg/dl)	.102*	-0.06	0.08	-0.09	-0.02	0.00	.106*	0.04	0.04	0.07
LDL (mg/dl)	-0.08	-0.02	0.02	-0.05	-.159**	-.160**	-.177**	-.146**	-.155**	-.128*
Triglycerides (mg/dl)	-.116*	0.05	0.02	-0.04	-0.01	-0.05	-.114*	-0.04	-0.06	-0.02
Systolic BP (mm Hg)	-0.04	0.01	0.01	-.106*	-.133**	-.126*	-0.09	-.148**	-.146**	-.112*
Diastolic BP (mm Hg)	-.123*	-0.02	-0.03	-0.05	-.130**	-.133**	-0.07	-.136**	-.140**	-0.09
Insulin (uU/ml)	-.136**	-0.05	-0.05	0.01	-.174**	-.170**	-.141**	-.191**	-.200**	-.186**
Glucose (mg/dl)	-0.03	0.08	0.00	0.00	-0.09	-.108*	-0.07	-.113*	-.114*	0.02
HOMA-IR	-.128*	-0.02	-0.05	0.01	-.176**	-.177**	-.141**	-.196**	-.205**	-.163**

Note. , IV= intradaily variability, IS = interdaily stability,** $p<0.01$, *$p<0.05$

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